HEALTH EFFECTS OF INORGANIC LEAD WITH AN EMPHASIS ON THE OCCUPATIONAL SETTING

AN UPDATE

by

Dr. J. N. Nearing
Medical Consultant
Health Studies Service
Ontario Ministry of Labour
400 University Avenue
Toronto, Ontario

1987

CONTENTS

		Page No.
List of Tables		iii
Table of Abbreviations		v
Note on International System of Units		vi
1. Summary of Recommendations		1
2. Executive Summary		3
2.1	Neurological Effects	3
2.2	Effects on Heme Synthesis and the Erythropoietic System	4
2.3	Reproductive Effects	5
2.4	Renal Effects	5
2.5	Miscellaneous Health Effects	6
3. Introduction		9
4. Update on the Metabolic Aspects of Inorganic Lead		11
4.1	Absorption	11
4.2	Distribution and Retention	11
4.3	Excretion	12
5. Health Effects of Inorganic Lead		14
5.1	Heme Synthesis and the Erythropoietic System	14
5.1.1	Heme Biosynthesis	14
5.1.2	Non-Erythropoietic Functions of Heme	17
5.1.3	Heme Biosynthesis and the Nervous System	18
5.1.4	Other Effects of Lead on the Erythropoietic System	18

CONTENTS (continued)

		Page No.
5.2	Nervous System	24
5.2.1	Neurobehavioural Effects	24
5.2.2	Neurophysiological Effects	41
5.3	Reproductive System	55
5.3.1	Animal Studies	55
5.3.2	Human Studies	59
5.3.2.1	Male Reproductive Function	59
5.3.2.2	Female Reproductive Function	60
5.3.2.3	Teratogenesis	61
5.3.2.4	Chromosomal Damage	62
5.3.2.5	Placental Transport of Lead	62
5.3.2.6	Prenatal and Perinatal Lead Exposure	63
5.4	Renal System	71
5.5	Hypertension	76
5.6	Carcinogenesis	86
5.7	Mortality	87
5.8	Immune System	90
5.9	Endocrine System	91
5.10	Clinical Symptomatology	92
6.	The Air Lead - Blood Lead Relationship	96
7.	Concluding Remarks	112
7.1	Neurological Effects	112
7.2	Effects on Heme Synthesis and the Erythropoietic System	113
7.3	Reproductive Effects	114
7.4	Renal Effects	115
7.5	Miscellaneous Health Effects	116
8.	Appendices	120
9.	References	126

List of Tables

			Page No.
1.	Introductory Table	Table of Abbreviations	v
2.	Table 5-I	PbB and Hemoglobin Levels	20
3.	Table 5-II	Quality Evaluation Questions for Studies of Neurobehavioural Function	36
4.	Table 5-III	Total Scores on Quality Evaluation Questions for Studies of Neurobehavioural Function	37
5.	Table 5-IV	Summary of Neurobehavioural Studies	38
6.	Table 5-V	Quality Evaluation Questions for Studies of Neurophysiological Function	50
7.	Table 5-VI	Total Scores on Quality Evaluation Questions for Studies of Neurophysiological Function	51
8.	Table 5-VII	Summary of Neurophysiological Studies	52
9.	Table 6-I	Mean Values and 95% Confidence Limits (C.L.) of Single Determinations of PbB Level Corresponding to Particular PbA Levels	100
10.	Table 6-II	Correlation Coefficient (R) of PbA vs PbB for Linear Regressions	101
11.	Table 6-III	95% Confidence Limits for the Predicted PbB Level for an Individual Worker for a Given PbA Level	103

List of Tables (continued)

			Page No.
12.	Table 6-IV	Expected Proportions of PbB at or Above Specified Levels Based on the Corresponding PbA Levels	103
13.	Table 6-V	Estimated % of Workers Having PbB Levels Above Specified Levels for Corresponding PbA Levels	104
14.	Table 6-VI	β Values for a Linear PbA-PbB Relationship	107
15.	Table 6-VII	Occupational Studies of the PbA-PbB Relationship	108
16.	Table 6-VIII	% of Workers Having Certain PbB Levels for a Given PbA Level	110
17.	Table 7-I	Blood Lead Level Ranges for First Detectable Biological Effects in Adults	117
18.	Table A-3-I	Relationship of Urine Lead Level to Blood Lead Level	124
19.	Table A-3-II	Predicted PbU (μg/L) Values for for Given PbB Values	125
		Predicted PbU (μg/g creatinine) Values for Given PbB Values	

Table of Abbreviations

ALA	delta-aminolevulinic acid
ALAD	delta-aminolevulinic acid dehydratase
ALAP	plasma aminolevulinic acid
ALAS	delta-aminolevulinic acid synthetase
ALAU	urinary delta-aminolevulinic acid
BUN	blood urea nitrogen
CPA	Center for Policy Alternatives (US)
EDTA	ethylene diamine tetraacetate
EPP	erythrocyte protoporphyrin
FEP	free erythrocyte protoporphyrin
GFR	glomerular filtration rate
IARC	International Agency for Research on Cancer
ICD	International Classification of Disease
MDI	Mental Development Index (Bayley Scales)
NAS	National Academy of Sciences (US)
NHANES	National Health and Nutrition Examination Survey (US)
OSHA	Occupational Safety and Health Administration (US)
Pb	lead
PbB	blood lead
PbU	urine lead
Py-5-N	pyrimidine-5'-nucleotidase
SCE	sister chromatid exchange
SI	International System of Units
SMR	standardized mortality ratio
TmG	renal tubular absorptive capacity of glucose
TWA	time-weighted average
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
ZPP	zinc protoporphyrin
μg	microgram
μm	micrometer
1,25-CC	1,25 dihydroxycholecalciferol

Note on International System of Units

The medical/scientific literature has not yet fully converted to the International System of Units (SI) respecting measurement of lead exposure. The majority of authors continue to use the μg/dl or μg/100 mL notation and they are generally cited using these units in this document. This utilization of a single measurement unit throughout was adopted to improve document clarity. In the summation and concluding remarks, the corresponding SI unit values are also given.

The conversion factor for inorganic lead (Pb) is:

$$1\ \mu g/100\ mL = 0.04826\ \mu mol/L$$

1. Summary of Recommendations

1.1 Based on the neurological changes documented, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

1.2 Based on the effects on the hemoglobin content of blood, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies in the range 50-60 μg/100 mL (2.4-2.9 μmol/L).

1.3 Based on the suspected prenatal neurotoxic effects and the requirement for prudence in exposing the developing conceptus to lead, the upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.4 μmol/L).

1.4 Based on the renal effects, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies below 60 μg/100 mL (2.9 μmol/L).

1.5 The upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

1.6 The upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.5 μmol/L).

1.7 Where ranges of blood lead level have been specified, from a prudent medical standpoint it would be preferable for the blood lead level to lie in the lower part of the range specified.

1.8 Consideration should be given to the lowering of the current action levels for lead in blood as set out in the Code for Medical Surveillance for Lead in Ontario in Ontario Regulation 536/81.

1.9 The upper limit for the concentration of lead in urine for adult lead-exposed workers which should not be exceeded lies in the range 6.3-11.2 μg/100 mL (0.30-0.54 μmol/L) or 33-73 μg Pb per g creatinine (0.16-0.35 μmol per g creatinine).

1.10 Based on the preceding recommendations and based on knowledge of the relationship between the concentration of lead in blood and the concentration of lead in air, consideration should be given to a lowering of the current air lead levels as set out in Ontario Regulation 536/81.

2. Executive Summary

Lead is a toxin with demonstrated multi-system effects in man. It has been extensively studied in the scientific literature and has been examined by a multitude of authors from numerous perspectives. Lead is a designated substance in the Province of Ontario and is regulated under Ontario Regulation 536/81 of the Provincial Occupational Health and Safety Act, Revised Statutes of Ontario, 1980. Since the proclamation of the lead regulation in 1981, many additional scientific studies respecting the health effects of lead exposure have been published. It is therefore prudent and timely to update the supporting health documentation for the Ontario lead regulation.

2.1 Neurological Effects

The neurological effects of inorganic lead exposure have been widely researched. Detectable changes in neuro-behavioural indices have been recorded in workers with blood lead levels in the range 40-60 μg/100 mL (1.9-2.9 μmol/L) and occasionally at lower levels. Changes in neurophysiological function, in particular slowing of peripheral nerve conduction velocities, have also been recorded in the range 40-60 μg/100 mL (1.9-2.9 μmol/L). It remains controversial as to whether these neurological changes represent adverse health effects. Dose-response relationships for neurological effects in otherwise asymptomatic workers have been demonstrated in the literature. From one perspective, lead-induced neurological changes may reasonably be interpreted as adverse health effects. The effects noted may be considered an early subclinical stage of clinical disease and have not been demonstrated to be reversible. They may also potentially enhance the susceptibility of the worker to the deleterious effects of other environmental influences.

Based on the neurological changes documented, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

A range for the blood lead level is chosen because the literature does not unequivocally support the choice of a precise value. Factors such as study design, including the choice of outcome measurements and measurement techniques, populations studied and biological variability are examples of possible reasons for the apparently inconsistent literature. From a prudent medical standpoint, it would be preferable for a worker's blood lead level to lie in the lower part of the range specified.

2.2 Effects on Heme Synthesis and the Erythropoietic System

Inorganic lead exposure adversely affects hemoglobin synthesis and red cell life span. The effects on hemoglobin are mediated via effects on the biosynthesis of heme, a complex organic component of hemoglobin and via the biosynthesis of globin protein. The effects of lead on heme biosynthesis are measurable as changes in several biochemical parameters which occur at blood lead levels less than 40 μg/100 mL (1.9 μmol/L). Interpretation of these biochemical changes as adverse health effects is also controversial, although perhaps more speculative than the interpretation of lead-induced subclinical neurological changes. A reduction in blood hemoglobin content represents an observable end point of the effects of lead on heme synthesis and the erythropoietic system. Although a reversible effect, reduction of hemoglobin content represents an early state of clinical disease and thus may reasonably be interpreted as an adverse health effect. A blood lead threshold for the lowering of hemoglobin content has not been conclusively established although the literature suggests that significant decreases in hemoglobin content occur for blood lead levels of 50-60 μg/100 mL (2.4 -2.9 μmol/L) in adults.

Based on the effects on the hemoglobin content of blood, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies in the range 50-60 μg/100 mL (2.4-2.9 μmol/L).

2.3 Reproductive Effects

Lead is a reproductive toxin in sufficient dose. Levels of lead exposure below those levels which may be associated with clinical lead poisoning (low dose lead exposure) have not been clearly associated with direct effects on the function of reproductive organs in either sex nor with teratogenic or mutagenic effects. The evidence presently available suggests that prenatal neurological fetotoxicity of low levels of lead exposure occurs in the approximate blood lead range 10-30 μg/100 mL (0.5-1.4 μmol/L). It is not presently possible to relate the postulated effects of prenatal lead exposure to early effects on the embryo or later effects on the fetus. In this context the term conceptus is used to cover all periods of human prenatal development. The conceptus is an actively developing organism, a fact which calls for prudence when considering an acceptable level of exposure of the conceptus to lead.

Based on the suspected prenatal neurotoxic effects and the requirement for prudence in exposing the developing conceptus to lead, the upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.4 μmol/L).

Lead crosses the human placenta. For practical purposes, limiting the blood lead level in the conceptus requires a similar limitation in the pregnant female.

2.4 Renal Effects

Lead exposure has been associated with the development of renal disease. An adequate dose-response function between blood lead level and renal function has not been defined for

chronic low dose lead exposure. The literature suggests that a blood lead level in the range 50-60 μg/100 mL maintained over time may be too high to protect workers from eventually developing clinically apparent kidney dysfunction.

Based on the renal effects, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies below 60 μg/100 mL (2.9 μmol/L).

2.5 Miscellaneous Health Effects

Concern exists regarding the association of blood lead level and blood pressure elevation. However, the current knowledge is inadequate to directly affect the setting of an upper limit of allowable lead exposure in the occupational setting based on the effects of lead exposure on blood pressure.

While certain lead salts are carcinogenic in some species of animals, there is inadequate evidence that lead is carcinogenic in man.

Mortality studies have confirmed the vulnerability of certain organ systems to lead, in particular the renal system. Inherent difficulties with the mortality studies do not permit dose-response relationships to be defined, therefore limiting their usefulness respecting the setting of an allowable level of lead exposure in the workplace.

The occurrence of clinical symptomatology at low levels of lead exposure confirms the possibility of organ dysfunction at these levels of exposure. However, the occurrence of symptoms is inadequate alone as a measure of lead exposure in the workplace.

The effects of lead on the endocrine and immune systems have been inadequately researched and any conclusions would be premature.

The upper limit of the blood lead level which should not be exceeded is taken to be the maximum level at which an adverse health effect is unlikely to occur either acutely or chronically as a result of exposure over a working lifetime. Controversy exists as to which observed biological changes associated with lead exposure are to be considered adverse health effects. Rational criteria associated with adverse or non-adverse health effects are outlined herein as guidelines and discussed in conjunction with the most relevant changes observed. The approach is taken that when observed biological changes may reasonably be interpreted to be adverse health effects, the prudent course is to treat them as though they were. Based on these considerations and the current scientific evidence detailed in this document, the following recommendations are made:

The upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

The upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.5 μmol/L).

Where ranges of blood lead level have been specified, from a prudent medical standpoint it would be preferable for the blood lead level to lie in the lower part of the range specified.

Consideration should be given to the lowering of the current action levels for lead in blood as set out in the Code for Medical Surveillance for Lead in Ontario in Ontario Regulation 536/81.

The monitoring of the amount of lead per unit volume of urine on single samples is a less reliable means of monitoring inorganic lead exposure than blood lead levels. Where the taking of blood lead levels is deemed impractical or impossible, the concentration of lead in urine has been used to monitor lead exposure.

The upper limit for the concentration of lead in urine for adult lead-exposed workers which should not be exceeded lies in the range 6.3 - 11.2 μg/100 mL (0.30 - 0.54 μmol/L) or 33 - 73 μg Pb per g creatinine (0.16-0.35 μmol per g creatinine).

It is not recommended that maternal urine lead monitoring be used to assess the lead exposure of the conceptus.

A relationship exists between the concentration of lead in blood and the concentration of lead in air. However, the lead exposure of the worker is dependent not only on air lead level but a number of other factors. It is reasonable to conclude that a reduction in the level of air lead will result in a reduction in the level of blood lead in the worker, although the amount of reduction may vary significantly between individual workers.

Based on the preceding recommendations and based on knowledge of the relationship between the concentration of lead in blood and the concentration of lead in air, consideration should be given to a lowering of the current air lead levels as set out in Ontario Regulation 536/81.

Because of the imprecise nature of the air lead-blood lead relationship, the setting of an appropriate air lead standard must be considered in a context broader than the nature of the air lead-blood lead relationship, and as such no specific recommendation regarding an appropriate air lead standard is made in this document.

A rational comprehensive consideration of the health effects of inorganic lead is an extremely difficult task. This document presents an overview of the current issues involving the health effects of inorganic lead. The intent is to serve as a foundation for making informed decisions regarding inorganic lead exposure in the workplace.

3. Introduction

Lead is a designated substance in the Province of Ontario and as such is regulated under Ontario Regulation 536/81 of the Provincial Occupational Health and Safety Act, Revised Statutes of Ontario, 1980. Since the proclamation of the lead regulation in 1981, many scientific studies respecting the health effects of lead exposure have been published. The objective of this document is to review the more recent scientific literature to determine whether the present regulation, its exposure limits and action levels appropriately reflect the current state of knowledge. For reference purposes, the relevant sections of the current regulation are listed in Appendix 1.

This report is meant to update the previous health effects document included in the Report on the Designation of Lead in Ontario prepared by the Occupational Health and Safety Division, Ministry of Labour, in 1981. As such it will not necessarily repeat certain basic information included in the previous report although some repetition will be required to establish continuity. Where necessary, earlier literature critical to the analysis will be discussed but the emphasis will be placed on literature subsequent to 1980. Material up to August, 1986 has been included in this review.

The focus of this review is designed to be the human health effects of lead with particular emphasis on the occupational setting. The source of information is the peer-reviewed published medical and scientific literature. Relevant papers will not only be cited but critically appraised with the intent to reach rational conclusions. In addition to original research, scientific reviews of the subjects of concern will also be examined and their conclusions considered herein. It is beyond the scope of this document to review all the published work on lead such as the extensive literature on the pediatric and environmental aspects of lead exposure. Furthermore it is not the intent of this report to critique in detail the massive number of

experimental animal studies regarding the toxicology of lead. Human studies are very extensive, targeted to a multitude of health effects and most directly relevant to the worker in an occupational setting. Where human studies are limited in number or are unavailable, unclear, or inadequate to suggest a dose-response relationship, relevant experimental animal research will be considered.

As multiple organ systems are involved, the review will be approached in a systematic fashion by category of physiological effect. Areas such as hematological and neurological research that have been more extensively studied or that are deemed more critical to the question of adverse health effects will be discussed in greater detail.

Reference is frequently made in the literature to low dose lead exposure. This is generally taken to mean levels of lead exposure below those levels which may be associated with clinical lead poisoning. In addition, the use of the term threshold level is used in this document to designate that level at which an effect is first detectable.

Organic compounds of lead have not been the same focus of research attention as has been inorganic lead. The recent literature reviewed relevant to regulatory considerations pertained to lead in its inorganic form. Any reference herein to "lead" is to be taken as inorganic lead unless specifically stated otherwise.

4. Update on the Metabolic Aspects of Inorganic Lead

Extensive revision of the physical, chemical and metabolic aspects of inorganic lead as previously described [1] is not required. This section will therefore not comprehensively review all aspects of lead metabolism but will only discuss more recent relevant publications.

4.1 Absorption

The literature continues to support an approximate absorption of 30-50% for inhaled lead and 5-15% for ingested lead in adults under normal nutritional conditions. Fasting increases the gastrointestinal absorption of lead whereas calcium and phosphate ingestion decrease absorption of lead by this route.

The rate of absorption of inhaled lead is directly dependent on the rate of deposition of lead particles in the respiratory tract. Although respiratory absorption has been thought to depend on the solubility of the inhaled lead compounds, Morrow et al. [2] have suggested that once deposited in the lungs of humans, lead particles are rapidly and completely absorbed regardless of apparent solubility, possibly due to chemical reactions *in vivo*.

4.2 Distribution and Retention

Lead absorbed into the body is distributed in a multi-compartmental fashion throughout the blood, soft tissue and bone. In excess of 99% of blood lead (PbB) is found within the red cells. Lead in soft tissues exchanges freely with the plasma component of lead in blood. Lead accumulation over time occurs in the body tissues, in particular the renal cortex and bone. Bone lead is not an inert depot and it is recognized that at least one skeletal compartment of lead is readily exchangeable [3]. This compartment serves as a continuing internal source of lead available to other soft tissue sites, even after lead exposure is discontinued.

Recently, Manton et al. [4] demonstrated a curvilinear relationship between the serum fraction of lead in blood versus whole blood lead levels. Similarly, at higher PbB levels, a greater relative proportion of lead in blood is found in plasma. It is from the plasma fraction of blood that lead diffuses into the body tissues. Thus the relative rate of diffusion of plasma lead into tissue increases with higher PbB levels since plasma lead represents a greater proportion of whole blood lead at these levels.

Because of the distribution kinetics of lead, a biological half-life is difficult to define. The actual biological half-life of lead in red cells is estimated to be 25 days based on isotope studies [3]. As discussed by Hryhorczuk et al. [5], the measured and therefore apparent half-life of lead in blood in non-isotope studies may range up to several hundreds or thousands of days, depending on age, length of exposure and period of follow-up. This reflects the multi-compartmental distribution kinetics of lead which allows constant interchange between lead in blood and lead in other body lead pools. O'Flaherty et al. [6] demonstrated a positive correlation between length of exposure to lead and the apparent half-life of lead in blood. This also reflects the multi-compartmental distribution kinetics of lead which allow for an increased body lead burden, particularly in bone, with increased length and level of exposure.

4.3 Excretion

The excretory aspects of lead metabolism have been previously discussed [1]. The predominant mode of excretion is renal involving glomerular filtration and tubular excretion. Excretion through the gastrointestinal tract also occurs. Of potential relevance in the occupational setting is the excretion of lead in breast milk. Wolff [7] reviewed a number of studies and reported a range of mean lead concentrations in normal human breast milk from 2 to 30 μg/L. A ratio of lead in milk to lead in blood of approximately 0.1 was reported in one lead-exposed worker

compared to an estimated ratio of 0.3 in the general population. Rabinowitz et al. [8] found breast milk lead content to correlate quite well with infant PbB levels at 6 months of age although milk lead levels accounted for only 10% of the variance in 6 month PbB levels. Lead levels in maternal milk correlated poorly with umbilical cord PbB levels. In summary, although lead transfer from blood to breast milk occurs, it appears that the partition of lead to milk is impeded, perhaps by the affinity of lead for hemoglobin or by the lower solubility of lead in the fatty components of breast milk.

5. Health Effects of Inorganic Lead

5.1 Heme Synthesis and the Erythropoietic System

One of the first measurable effects of lead is on heme synthesis. Heme is a complex organic compound ultimately incorporated into the hemoglobin molecule and directly involved with oxygen transport in the blood. The function of heme is not restricted to the blood. It is an integral part of certain enzyme systems which have a host of functions in other areas such as the nervous, hepatic and musculoskeletal systems. Within the erythropoietic system, lead also influences globin protein synthesis and effects a shortening of red cell survival time.

5.1.1 Heme Biosynthesis

The effects of lead on heme biosynthesis has been widely studied in both animals and humans. Major enzymes involved include delta-aminolevulinic acid dehydratase (ALAD), ferrochelatase, and delta-aminolevulinic acid synthetase (ALAS).

The literature on inhibition of ALAD is extensive and has been reviewed in detail in a number of documents (9,10,11,12). ALAD activity is quite sensitive to inhibition by lead which is observed at PbB levels of 10-15 μg/100 mL. It has been proposed that the threshold PbB level for the effect of lead on ALAD in humans is zero and that ALAD activity is inhibited to some extent at virtually all PbB levels.

Stimulation of mitochondrial ALAS has been found in lead-exposed animals and workers. The threshold for stimulation of ALAS is somewhat higher than that for suppression of ALAD, the former occurring at a PbB level of approximately 40 μg/100 mL [13].

Ferrochelatase is an enzyme involved in the insertion of iron into a heme precursor, protoporphyrin IX. As

ferrochelatase is directly inhibited by lead, excessive accumulation of protoporphyrin, as erythrocyte protoporphyrin (EPP) takes place in red cells. The majority of this protoporphyrin acquires a zinc ion forming zinc protoporphyrin (ZPP) which is tightly bound within red cells. It is estimated that 95% of the protoporphyrin in red cells is ZPP whereas 5% is not bound, i.e., free erythrocyte protoporphyrin (FEP). Protoporphyrin accumulation in lead-exposed individuals can be secondary to either direct ferrochelatase inhibition or impaired mitochondrial iron transport which makes less iron available for heme biosynthesis within the mitochondrion.

During periods of lead exposure, the PbB level represents more recent lead exposure and absorption, whereas ZPP levels represent the effects of lead exposure and absorption for approximately 3 - 4 months prior to measurement. This partly reflects the tight binding of ZPP within red cells in combination with the average red cell life span. A delay therefore occurs between the response of ZPP and changes in lead exposure levels.

Blood protoporphyrin levels are exponentially related to PbB levels in both adults and children [10]. Several authors have estimated that the PbB threshold range for EPP elevation in adults is between 25-35 μg/100 mL [14,15,16,17,18]. The PbB threshold for EPP elevation in adult females is less than that for adult males whereas the levels for children are less again. Roels et al.[18] found significant elevations of FEP in females at PbB levels above 20 μg/100 mL. Piomelli [19] showed for urban children with a PbB level less than 30 μg/100 mL that the mean PbB threshold for EPP elevation was 16.5 μg/100 mL. The known threshold for blood protoprophyrin elevation and the exponential rises of blood protoporphyrin levels above 40-50 μg/100 mL in adults limit the usefulness of protoporphyrin levels as a stand-alone means of monitoring occupational lead exposure, particularly at lower levels of lead exposure.

The combination of ALAS stimulation and ALAD inhibition results in excess delta-aminolevulinic acid (ALA) accumulation and an increase in urinary ALA excretion. Elevation of circulating ALA precedes elevation of urinary ALA. Meredith et al. [13] found urinary ALA levels to be exponentially related to blood ALA levels which in turn were also exponentially related to PbB levels. Both relationships approached linearity at lower levels of lead exposure. The data suggested the existence of a linear relationship between urinary and blood ALA levels at PbB levels below 40 μg/100 mL. Meredith et al. [13] suggested that above PbB levels of 40 μg/100 mL accelerated rises of ALA synthesis occur. An individual worker may show wide normal biological variation in urinary ALA on random sampling. More reliable results are obtained with 24 hour urine collections. Increased urinary excretion of coproporphyrin, a metabolite involved in the heme biosynthesis pathway, also occurs in lead-exposed individuals. This is secondary to either accumulation of the substrate protoporphyrin or to enzyme inhibition of the heme biosynthesis enzyme coproporphyrin oxidase or a combination of both mechanisms.

The effects of lead on heme biosynthesis are influenced by the body iron status of the individual reflecting the involvement of iron as a component of heme. Iron deficiency causes an increase in EPP levels as a result of insufficient iron substrate being available for heme biosynthesis. The occurrence of iron deficiency in association with lead exposure results in greater elevation of EPP levels than either condition alone [20]. Altered kinetics of the mitochondrial enzyme ferrochelatase are believed to be the basis for this interaction. Iron status of an individual may therefore be a confounding influence regarding the use of blood protoporphyrin levels as a means of monitoring occupational lead exposure.

5.1.2 Non-Erythropoietic Functions of Heme

As well as being an integral part of the hemoglobin molecule, heme is an essential component of other complex proteins, in particular the cytochrome enzyme systems. Renal cytochrome systems are involved with vitamin D metabolism. Vitamin D is ultimately hydroxylated to 1,25-dihydroxycholecalciferol (1,25-CC) in the kidney. Mahaffey et al. [21] have demonstrated a significant negative association between serum 1,25-CC and PbB levels in the range 12-59 μg/100 mL for children aged 1-16 years. Above a PbB level of 60 μg/100 mL, serum 1,25-CC levels were severely depressed. Greenberg et al. [22] found no consistent abnormalities of serum calcium, phosphorus or vitamin D or 1,25-CC levels in 38 lead-exposed workers who may have been heavily lead-exposed in the past but had a current mean PbB level of 32 μg/100 mL. In addition to the stimulation of gastrointestinal calcium absorption via the formation of calcium-binding protein, 1,25-CC is believed to have several physiological actions at the cellular level. These include involvement in cellular calcium homeostasis, cell differentiation and immuno-suppression. The impact of lead on regulation of calcium metabolism as mediated by its effect on vitamin D metabolism is not fully understood and is an area of active research. Current knowledge does indicate that through its effects on vitamin D metabolism, lead has the potential for metabolic effects at multiple organ sites. The function of the hepatic mixed-function oxygenase system in humans is also affected by lead exposure. Components of this system include the cytochrome P450 enzymes whose function in hepatic drug metabolism is inhibited by lead. Saenger et al. [23] have demonstrated alterations of steroid metabolism in children with previous lead exposure and mean PbB levels of 46 μg/100 mL. This alteration was manifested as decreased hydroxylation of cortisol which is mediated by a hepatic cytochrome microsomal enzyme system.

Children are developing organisms and demonstrate differences from adults in certain physiologic mechanisms

and ability to cope with physiologic stress. Specifically, differences in the metabolic effects of lead have been demonstrated. The ultimate health effects of these non-erythropoietic effects of lead on heme synthesis remain unclear and findings in children may not necessarily be extrapolated to adults. However, it is clear that through its effects on heme synthesis, lead has the potential to affect a number of organ systems.

5.1.3 Heme Biosynthesis and the Nervous System

A causal association between changes in heme biosynthesis and the neuropathy of lead poisoning has been proposed. Silbergeld et al. [24] discussed two unproven hypotheses in this area. The first hypothesis is that the neuropathy is secondary to an excess accumulation of the postulated neurotoxin ALA or its metabolites. The second hypothesis is that the disordered function of the nervous system results from abnormal heme biosynthesis within nerve cells. Hammond et al. [25] examined the relationship between 14 subjective symptoms of a neurological nature and PbB level, urinary ALA (ALAU) and plasma ALA (ALAP). ALAU and ALAP levels correlated better than PbB level with the neurological symptoms although less than 50% of the effects on neurological symptomatology were explained by variation in ALAU or ALAP levels. This study cannot be considered confirmation of a relationship between ALA and neurotoxic effects.

A detailed discussion of the inconclusive complex biochemical mechanisms of lead neurotoxicity is of lesser relevance to occupational regulatory considerations than an elaboration of the neurological clinical sequelae of lead exposure. This will be further discussed in Section 5.2.

5.1.4 Other Effects of Lead on the Erythropoietic System

Apart from effects on heme synthesis, lead is known to affect the synthesis of the globin portion of the hemoglobin

molecule. This is believed to be secondary to inhibition of globin synthesis due to heme deficiency as well as to direct inhibition of globin synthesis. Excessive exposure to lead also results in a shortening of the red cell life span. Hernberg [26] demonstrated a statistically significant negative correlation between PbB level and red cell survival time. The data were not conclusive but suggested a threshold level for shortening of red cell survival below a PbB level of 60 μg/100 mL.

The anemia associated with lead exposure is the clinical result of both decreased hemoglobin production and shortened red cell survival. The PbB threshold for the lowering of hemoglobin level has not been conclusively established. A review by Moore et al.[10] concluded that hemoglobin concentrations do not fall until the PbB level reaches 60 μg/100 mL or above. Grandjean [27] demonstrated a negative correlation of hemoglobin level with PbB levels below 50 μg/100 mL. Baker et al.[28] found that a total of 21% of lead-exposed workers had hemoglobin levels less than 14.0 g/100 mL, although no comparative results with non lead-exposed workers were given. A breakdown of the results found in both studies is given in Table 5-I. Valentine et al. [29] found no difference in hematocrit values between 69 lead-exposed workers (mean PbB level 61.3 μg/100 mL) and controls (mean PbB level 22.0 μg/100 mL). The significance of these cross-sectional data is dependent on the variance of normal human hemoglobins; 14.0 g/100 mL may be normal for one individual whereas 16.0 g/100 mL may be normal for another. The ranges obtained from cross-sectional analyses become less meaningful in this context. Smoking histories may seriously confound comparisons of hemoglobin levels. Hemoglobin or hematocrit levels may also be influenced by blood dilution which may be due to a number of causes. It would be preferable to measure the change of hemoglobin, or preferably hematocrit, over time compared with measures of lead exposure. In the Valentine et al.[29] study, a subgroup of workers with at least one year of lead exposure did not have significantly different hemoglobin levels at

the time of testing compared to known hemoglobin levels at initial employment. Only 12 workers were involved in this comparison and mean PbB values ranged widely from 26.4 to 68.4 μg/100 mL. Hematocrit values of the entire exposed group did not differ significantly over 12-18 months but systematic analytical error in the biochemical measurements was probable as evidenced by inter-laboratory quality control measurements. Earlier work by Tola et al.[30] revealed a significantly lower mean hemoglobin in a group of 33 newly employed battery plant workers (mean PbB level 50 μg/100 mL) after 100 days of lead exposure.

TABLE 5-I
PBB AND HEMOGLOBIN LEVELS

Investigator	Range of PbB (μg/100 mL)		
	<25	25 - 60	>60
Grandjean [27] (N = 202) % of workers within specified range having Hemoglobin < 14.5 g/100 mL	17%	26%	45%
	40 - 59	60 - 79	>79
Baker et al. [28] (N = 129) % of workers within specified range having Hemoglobin < 14.0 g/100 mL	5%	14%	36%

The threshold PbB level for a change in hemoglobin concentrations for children is believed to be lower than that for adults. In a review of the health effects of lead, the World Health Organization (WHO) [11] concluded that a reduction in hemoglobin may occur in some children with PbB levels of 40 μg/100 mL. Betts et al. [31] found a

significant negative correlation between hemoglobin level in children and PbB level. Anemia, defined as a hemoglobin level less than 11 g/100 mL, occurred in 36% of children with PbB levels between 37-60 μg/100 mL and 14% of children with PbB levels less than 37 μg/100 mL. In children, the presence of iron deficiency potentiates the effect of lead on hemoglobin concentration by both a direct effect on the kinetics of the enzyme ferrochelatase and by increasing lead absorption from the gastrointestinal tract. The occurrence of iron deficiency is therefore a possible confounding factor in studies of the effect of lead on hemoglobin concentrations of children. An approximation of the threshold value of PbB at which measurable effects on hemoglobin concentrations in children occur is 40 μg/100 mL although this has not been conclusively established.

Other less well understood hematological effects are associated with excessive lead exposure. These effects include the occurrence of basophilic stippling and inhibition of the activity of the enzyme pyrimidine-5'-nucleotidase (Py-5-N) [10,32,33]. This enzyme is involved with red cell stability and survival time and is hypothesized to be involved in globin chain synthesis. Also believed related to decreased red cell survival is lead-induced inhibition of the enzyme glucose-6-phosphate dehydrogenase (G6PD) as demonstrated in vitro by Lachant et al.[33] These changes remain areas of active research and conclusions with respect to health effects in humans would be premature.

In Summary: It is clear that lead intoxication adversely affects hemoglobin synthesis and red cell life span. The effects on hemoglobin are mediated via effects on the biosynthesis of heme and globin protein. Enzymes involved in heme biosynthesis which have been well studied in relationship to lead include ALAD, ALAS and ferrochelatase. The threshold level of PbB for observable effect on ALAD ranges from 0 - 15 μg/100 mL and is estimated to be 40 μg/100 mL for ALAS. Inhibition of ferrochelatase results

in erythrocyte protoporphyrin (EPP) accumulation either as zinc protoporphyrin (ZPP) or free erythrocyte protoporphyrin (FEP). The threshold PbB level for elevation of EPP in adults ranges from 20-35 μg/100 mL and for children is estimated to be 16 μg/100 mL. Excretion of ALA in the urine rises exponentially above a PbB level of 40 μg/100 mL but the threshold PbB level for ALA excretion in the urine has not been clearly established.

The studies relating PbB level to hemoglobin level are inconsistent. Although a PbB threshold for the lowering of hemoglobin level has not been conclusively established, the literature suggests that decreases in hemoglobin content may occur at PbB levels of 50-60 μg/100 mL in adults and probably at lower levels for children. However, this does not necessarily imply the occurrence of a clinically symptomatic anemia.

Effects of lead on vitamin D metabolism and hepatic enzyme systems (steroid metabolism, drug detoxification) have been demonstrated. The effects of lead on heme synthesis have been postulated as a mechanism for the neurotoxic effects of lead.

An essential consideration at this point is whether these numerous effects associated with lead are to be considered adverse health effects. The question of adverse versus non-adverse health effects has been considered by the US National Academy of Sciences (NAS) [35]. Their criteria used to define adverse and non-adverse health effects are attached as Appendix 2. These criteria are incorporated herein as guidelines for discussion only and not as absolute standards.

The health significances of inhibited ALAD activity, ALAS stimulation and ALA accumulation are not clear. Accumulation of EPP as ZPP or FEP represents evidence of an adverse effect on heme and hemoprotein synthesis. In the light of the NAS statement, the current knowledge respecting

these biochemical changes does not justify their classification as adverse health effects. However, they cannot be classified with certainty as non-adverse health effects, although one might judge them to more closely approximate the categories of this classification. From a different perspective, one may conclude that none of these heme-related biochemical effects can be considered significant until the effects are ultimately reflected in a change in the clinically measurable end product of the biochemical pathways. In this light, a decrease in hemoglobin content or hematocrit level can be considered an adverse health effect. From yet another perspective, any measurable biochemical perturbation may be considered by some to represent adverse health effects.

Impairment of vitamin D production may ultimately affect metabolic function in various human tissues. The reviewed literature has discussed the effect of lead on vitamin D metabolism in children and not in adults. The relevance of this effect to adults in the occupational setting is not clear. It might be postulated that the effect of lead on vitamin D metabolism in the fetus of a pregnant worker would be similar to that in children. However, the potential availability of vitamin D or its metabolites from maternal blood could confound this postulate and extrapolation directly between effects on vitamin D metabolism in children and vitamin D metabolism in the fetus would be unwise.

In Conclusion: Lead exposure has well documented effects on heme synthesis both within and outside the erythropoietic system. It also affects globin protein synthesis and red cell survival. An endpoint which reflects these biochemical alterations is the reduction of hemoglobin content in the blood. The literature is inconclusive as to the PbB level at which this occurs, but suggests that reduction of hemoglobin content in adult workers may occur at PbB levels of 50-60 μg/100 mL and that hemoglobin is negatively correlated with PbB levels in this range. The PbB threshold for the occurrence of several heme-related biochemical

effects is less than 50 μg/100 mL, although it remains controversial as to whether these changes represent adverse health effects.

5.2 Nervous System

Neurobehavioural and neurophysiological studies of the effects of lead exposure are two areas of particular interest that have emerged in the literature in recent years. The neurophysiological studies have emphasized the study of nerve conduction parameters.

5.2.1 Neurobehavioural Effects

Repko et al. [36] published an extensive critical review in 1979 of the neurological and behavioural sequelae of inorganic lead absorption. The authors concluded that neurological and behavioural changes occur in the early stages of lead poisoning before the onset of classical symptoms. Prior to 1970 it had been generally assumed that clinical evidence of lead poisoning rarely, if ever, appeared at PbB levels below 80 μg/100 mL whole blood. Newer work began to suggest that identifiable clinical signs or symptoms occurred at PbB levels of 60 μg/100 mL or less and case reports appeared with clinical symptoms demonstrated repeatedly at PbB levels below 80 μg/100 mL. Repko et al. [36] hypothesized that the clinical and neurobehavioural sequelae of inorganic lead exposure represented a continuum of dysfunctions experienced by all exposed individuals to a greater or lesser extent. In their exhaustive review, the authors concluded:

> "Recognition of impaired neurobehavioural functions as early stages of disease provides valid evidence to support the contention that inorganic lead exposure at or below currently accepted safe levels may result in reduced functional capacity, and therefore, material impairment of health."

Literature subsequent to 1980 will now be considered in some detail. Research data from several recent studies provide a basis to estimate dose-response levels for neurobehavioural toxicity.

Valciukas et al. [37] performed a cross-sectional survey of 3 groups of men with variable exposure to lead and one group not occupationally exposed. Statistical corrections were made for age and education level. For smelter workers (mean PbB level 51.2 μg/100 mL), a statistically significant negative correlation between one psychometric test (Weschler Adult Intelligence Scale (WAIS) Block Design Test) and PbB level was obtained. For this group, the blood ZPP level was significantly correlated with all corrected psychometric scores. The authors concluded that workers chronically experiencing lead levels previously accepted as safe were at risk of developing brain dysfunction. The findings suggested that the higher the degree of lead absorption, the higher the degree of risk of brain dysfunction. PbB determinations were not made on the unexposed group nor was it clear how the workers were chosen for the study. Despite these problems in study design, this work is suggestive of an association between a PbB level of approximately 50 μg/100 mL and a reduction in neurobehavioural functioning.

In a cross-sectional study of 9 men with PbB levels ranging from 60-80 μg/100 mL, Arnvig et al. [38] found normal intellectual potential but impairment of memory, attention, concentration, and psychomotor performance on standard intelligence testing. The method of sample selection, sample size and absence of control groups make definite conclusions from this work inappropriate.

In an attempt to define a critical threshold level for the effect of lead exposure on CNS functioning, Mantere et al.[39] carried out a prospective study of 24 storage battery plant workers first starting occupational lead exposure. The authors demonstrated a significant

deterioriation of standard tests of psychological performance (WAIS Block Design, Santa Ana coordination) in the lead workers at one and two year re-examinations compared to age- and sex-matched controls not occupationally exposed to lead. At the one and two year re-examinations an additional psychological test of memory and concentration (Digit Span Test) was performed and yielded a statistically significant group difference. The subjects and controls were not matched for socioeconomic status nor education level and only 16 (18%) of the subjects remained after two years. The significance of this loss to follow-up is potentially serious if there existed an association between intelligence and/or psychological test scoring ability and the decision to continue working in the battery plant. The PbB levels of the lead-exposed group increased from an initial 15.3 ± 6.7 μg/100 mL to 30.5 ± 9.6 μg/100 mL after 2 years and for the control group remained the same at 10.5 ± 3.7 μg/100 mL and 10.3 ± 4.0 μg/100 mL. Even though this study has significant drawbacks, it benefits greatly from being a controlled prospective study done on workers first entering lead exposure. The authors concluded that impairment in the function of the central nervous system is caused by "really low levels of lead exposure". The study could define no exact threshold between a no-effect and a risk level for lead exposure.

Subsequently, Mantere et al. [40] reported a four year follow-up on the same group of workers. Only 11 workers of the original 89 (12%) were re-examined after four years. The PbB levels for the exposed group were 15.3, 30.3, 30.5, and 28.8 μg/100 mL at time zero, one, two and four years respectively. The corresponding unexposed group mean PbB levels were 10.6, 10.6, 10.4 and 6.8 μg/100 mL. There were no PbB values over 48 μg/100 mL in the exposed workers and no PbB values over 21 μg/100 mL in the control workers. Some inconsistency was noted at the four year mark in that the performances of both the exposed and the control groups had deteriorated, whereas the control group had shown improved performance during the first two years of follow-

up. An internal comparison was done by dividing the lead-exposed workers into two groups using the median time-weighted average (TWA) of the PbB values (approximately 27 μg/100 mL) as the dividing point. There were no significant changes in the test results of the low lead group during the first year, but slight deterioration of visuomotor performance was detected in the high lead group. No significant differences within the exposed group were observed at the four year mark, although the statistical tests of significance lose meaning in light of the small numbers of subjects involved. It must be noted that the psychological performance impairments were slight and indeed all test scores remained within the normal range of variation, presumably compared to standard scores for corresponding groups of individual workers. Affected performances related largely to visual intelligence and visuomotor functions. The findings did not support the existence of a strong linear relationship between PbB level and psychological performances for the range of PbB levels studied due to the variability of the results in the exposed workers. Individual differences in response and intervening confounding variables such as worker motivation could have masked toxic effects of lead on performance. The authors concluded that higher nervous functions were affected by rather low levels of exposure. More changes were noted to have occurred in workers whose PbB level was over 27 μg/100 mL compared to those workers whose corresponding PbB values remained below this level.

Another important series of reports was published by Baker et al. [41,42,43] Lead-exposed foundry workers and controls were evaluated using a comprehensive set of neurobehavioural tests. An attempt was made to overcome selection bias by testing 91% of exposed workers. Adjustment was made for age, gender and education in a multiple linear regression analysis. The authors noted increased reporting of "worker tiredness" and "trouble remembering" in workers' groups having PbB levels exceeding 60 μg/100 mL compared to a referent population selected from an assembly plant adjacent

to the foundry. Based on mood testing using the Profile of Mood States (POMS), increased rates of depression, confusion, anger, fatigue and tension were reported among workers with PbB levels over 40 μg/100 mL compared to the unexposed group. Impairment of neurobehavioural function was found in performance on tests of verbal concept formation and selected memory tests. No statistical analyses were initially reported [41] but were subsequently presented and were significant for a number of parameters in a more elaborate report using the same data [42]. Psychological assessments were done in-plant, thereby allowing examiners to identify lead workers. Examiners were therefore not fully "blind", although they did not know individual PbB levels. The authors concluded that lead exposure in adults causes dose-dependent impairment of neurobehavioural function and that initial signs of lead toxicity in adults become manifest in the central nervous system as abnormalities of memory, psychomotor function and abstract concept formation before overt disruption of the peripheral nervous system occurs. The authors concluded that the dose-response relationship suggested significant adverse neurobehavioural effects in adults with PbB levels between 40-60 μg/100 mL.

In a three year follow-up report on this same group of workers, Baker et al. [43] evaluated the reversibility of behavioural toxicity secondary to a reduction in lead exposure which resulted from a new lower workplace standard as set by the United States government. In the second year of the study using multiple regression analyses the authors demonstrated significant associations between lead absorption indices and standard tests of memory, visuomotor function and mood disturbances. After exclusions and losses to follow-up, the number of exposed and unexposed workers available for analysis in the third year were 36 (34%) and 14 (22%) respectively. None of the exposed workers in this later analysis had a PbB level greater than 50 μg/100 mL. As a result of reductions in lead exposure, the PbB level of the study population fell and was associated with a

reduction in the severity of mood disturbances compared to their earlier state. Workers whose PbB levels were at least 50 μg/100 mL on first testing experienced considerable subsequent reduction in their reports of tension, anger, depression, fatigue and confusion. None of the changes in test performances were statistically significant because of the small number of observations. Other indices of verbal ability, memory and visuomotor function did not show any signficant corresponding change with reduction of PbB level. The authors postulated that this may have been due to an inadequate follow-up period compared to the time required for reversibility of the psychometric changes. Selection bias resulting in the placement of workers with poorer memory and poorer psychomotor function in higher lead exposure jobs is an alternate explanation of these results. Although having a high fall-out rate and having possible information bias due to worker awareness of their exposure category, this is one of the better studies from an epidemiological standpoint. The authors performed a prospective analysis with standardized outcome indices using built-in tests for reproducibility and included statistical adjustments for age, sex, education, parental socioeconomic status and alcohol consumption for control of major confounders. They concluded that workers with PbB levels between 40 and 60 μg/100 mL displayed behavioural toxicity in the initial analyses and that PbB levels should remain below 40 μg/100 mL if behavioural toxicity of chronic lead exposure is to be prevented.

Hogstedt et al. [44] studied 49 workers with an average exposure to lead of 18 years. Poorer performance was demonstrated in 11 of 14 non-verbal psychological tests with significant differences in memory, learning and reaction time compared to a referent group of male industrial workers whose PbB level had never exceeded 21 μg/100 mL. The TWA-PbB level for the lead-exposed workers was between 27 and 68 μg/100 mL. The psychological test battery used was not directly comparable to other American and British tests, being a Swedish test battery standardized to the Swedish

general population. The exposed group reported significantly more symptoms than the comparison group. The authors divided the exposed subjects into high (TWA-PbB level above 52 μg/100 mL) and moderate exposure (TWA-PbB level 27-52 μg/100 mL) groups. For the moderately exposed group, significant differences were obtained for memory and learning compared to the referent group whereas reaction time was significantly decreased for the high exposure group compared to the referents. No significant linear correlations were found although a non-linear dose-effect relationship was suggested. The exposed group and referents were comparable in age, sex and educational background. However, there existed the possibility of selection bias, information bias, worker self-selection over time and uncontrolled confounders such as socioeconomic status and prevalence of alcoholism. Regardless, this work rates serious consideration and lends international consistency to the findings of other researchers. The conclusion was made that central nervous system impairment occurs with PbB levels from 48 to 52 μg/100 mL and that the average PbB level should be below 52 μg/100 mL to avoid these adverse health effects.

Another cross-sectional analysis was done by Campara et al. [45] who studied male workers having PbB levels in the range 46-60 μg/100 mL and whose PbB levels were never known to have exceeded 60 μg/100 mL. Two comparison groups were used, one with no occupational lead exposure and an exposed group whose current PbB levels were below 35 μg/100 mL and where PbB levels were never known to have exceeded 40 μg/100 mL. The exposed group of workers with the higher PbB levels showed significantly poorer test performance on standardized psychological tests. An analysis of test components suggested that poorer test performance was related to impairment of general functioning with a lesser deterioration in the specific functions of verbal reasoning and abstraction. The lead-exposed workers with the higher PbB levels reported more physical symptoms than the two comparison groups. Significant correlations of PbB level with perceptual and psychomotor tasks and verbal abstraction

and comprehension were found. Zimmerman-Tansella et al.[46] reported psychological symptomatology (as measured by questionnaire) in these same workers to be insensitive to low levels of lead exposure. A significant difference was found between physical (gastrointestinal, neurological) symptoms in workers with PbB levels ranging from 46 to 60 μg/100 mL compared both to controls and exposed workers with PbB levels less than 35 μg/100 mL. For the exposed workers, a significant positive correlation was found between lead uptake as measured by PbB level and the number of reported physical symptoms but not psychological symptoms.

Parkinson et al. [47] compared 288 randomly chosen lead-exposed workers to 181 non-lead-exposed industrial workers. Eight clinically validated psychosocial and ten neuropsychological parameters were examined. The mean PbB level was 40 μg/100 mL for the exposed workers with only 23% of these workers having had previously recorded PbB levels greater than 60 μg/100 mL. Current PbB levels for controls were less than 35 μg/100 mL but the actual values were not given. The degree of separation of PbB levels between the two groups is therefore unclear. The exposed workers were similar to the non-exposed workers on most of the psychosocial and neuropsychological measures. The authors found similar results for workers with longer term exposure in a separate analysis. Measures of prior and current lead exposure were found to be unrelated to neuropsychological test scores. The dose-response relationship was analyzed in a multiple regression analysis which demonstrated a meaningful association between exposure and level of interpersonal conflict, a psychosocial parameter. The authors noted consistency of their findings with previous reports of aggressive behaviour and hostility in lead-exposed workers. They concluded that lower lead exposure levels do not appear to affect cognitive functioning but are somewhat related to psychosocial functioning. Despite this conclusion, they stated that their study gave evidence against hypotheses suggesting adverse neuropsychiatric

effects of low level lead exposure presumably because the psychosocial effects were quite small. A potentially serious source of selection bias is that workers with greater alteration in the parameters measured may have been unable to continue in lead-related work leaving behind a self-selected group of healthier workers. A negative check of compensation records for neurological damage in lead-exposed workers was cited as a defence against this bias. It is not clear which records were checked nor if workers with the low levels of lead exposure found in this study would have registered compensation claims for a lead-related disability.

Araki et al. [48] recently studied psychological performance and its relation to central and peripheral nerve conduction in workers exposed to lead, zinc and copper. Mean PbB levels in exposed and control workers were 42 and 13 μg/100 mL respectively (ranges 16 - 64 μg/100 mL and 8 - 20 μg/100 mL respectively). Plasma zinc and copper levels were significantly higher in exposed workers compared to controls. Five WAIS subtests were examined but only one (picture completion) was significantly decreased in exposed as compared to control workers and a significant correlation of PbB levels with this subtest was found. Of note, the authors found significant correlation of the score on picture completion with nerve conduction time in the spinobulbar region as measured in the neck and basal brain area. No such correlation was found with measurement of conduction time taken more peripherally in the upper arm and shoulder area. The authors suggested that alterations in psychological performance in lead-exposed workers were more closely related to central nervous system function than peripheral nervous system function. This suggests that psychomotor dysfunction in lead-exposed workers is not simply a result of peripheral nervous system dysfunction. No significant effect of zinc or copper on psychological function was found. This study is further discussed in Section 5.2.2 both with respect to neurophysiological function and the inherent weaknesses in the study which require caution in the interpretation of results.

Williamson et al. [49] approached the question of the neurobehavioural effects of low level lead exposure from another perspective, using a different test battery from those commonly used in other studies. They examined the information processing abilities of lead-exposed workers compared to non-exposed controls. Information processing theory provides for the development of a battery of performance tests which attempt to assess specific stages of information processing including initial perception, psychomotor function and short- and long-term memory. Included in the battery are physiological tests of performance and perception, objective measures reasonably independent of education level. Fifty-nine lead-exposed workers were examined (mean PbB level 48.9 μg/100 mL, range 24.7-81.2 μg/100 mL) and compared to 59 matched controls with no history of any toxic exposures. No measures of lead exposure were taken for the control group. Visual sensory function, psychomotor tasks and cognitive functions were significantly more poorly performed in the lead-exposed workers. Perhaps due to the homogeneity of the lead-exposed workers, multiple regression analysis failed to show any association between measures of exposure and performance with the exception of one short-term sensory memory test. This study supports the findings of other positive neurobehavioural studies using different assessment techniques. It also suggests that visual sensory perceptual input may be one of the initial processing functions affected by low level lead exposure.

There is little scientific information respecting the reversibility of the neurobehavioural effects of lead in man. Consideration of the experimental animal studies is helpful regarding this issue. Silbergeld [50] reviewed and summarized relevant findings of experimental animal studies of lead neurotoxicity. She concluded that the experimental evidence strongly suggested that lead is an irreversible neurotoxin in animals. This was based on evidence indicating persistent effects of lead exposure on neurobehavioural function long after cessation of exposure.

Related to this is the persistence of lead in the brain tissue of animals after lead exposure has ended. Chelating agents were found to have little effect on the removal of lead from the brains of rodents. In vitro studies have suggested that intracellular lead is not removable by chelating agents from brain cells. Rice et al.[51] dosed monkeys orally with lead from birth until 200 days of age. Three groups of animals were studied with PbB levels of 25, 15 and 3 μg/100 mL from 0-200 days of age followed by measured steady state PbB levels of 13, 11, and 3 μg/100 mL thereafter. At three years of age, learning as measured by improvements in behavioural performance of the monkeys correlated negatively and significantly with lead dose, suggesting that lead-induced neurobehavioural changes may be long-lived in monkeys after removal from experimental lead exposure. The evidence in man is insufficient to permit any conclusion respecting the reversibility of the neurotoxic effects of lead.

In addition to ongoing critical appraisal, some standardization of the evaluation of the epidemiological studies has been attempted by applying a list of evaluative questions (Table 5-II) to the articles reviewed. These questions are not part of a standard protocol but have been generated by the author to address certain basic questions of study design. The scores are attached as Table 5-III, and are intended to be used for general comparisons between studies. Table 5-IV gives a summary of the results of the studies reviewed.

In Summary: Although there has been variance in the recent literature respecting the degree and type of neurobehavioural outcome, the studies are generally consistent regarding the occurrence of measurable neurobehavioural changes in association with lead exposure. Workers have been examined at first exposure to lead and after long-term exposure. Detectable negative changes in neurobehavioural indices have been recorded in workers with PbB levels in the range 40-60 μg/100 mL and occasionally at lower levels.

The question of whether these neurobehavioural changes represent adverse health effects must be addressed. It is useful to again consider the criteria of Appendix 2 as guidelines for adverse and non-adverse health effects. Parkinson et al. [47] have suggested that the actual scores obtained in neurobehavioural studies of low level lead exposure are not indicative of impaired functional capacity as represented by clinical brain dysfunction since the performance scores were largely within the normal range. The nature of the comparative populations used to define the normal range is not precisely clear although it probably represents some component of the general population. Given a rather wide range for normal neurobehavioural function, the functioning of a worker towards the lower end of the range may in itself represent a handicap. It would seem the observation of a change in function is the critical point. Documentation of a significant change in neurobehavioural function, although perhaps within a normal range, might be considered a very early stage of clinical lead encephalopathy. A dose-response relationship for central nervous system effects in otherwise asymptomatic workers is indicated in the literature. Neurobehavioural effects have not been shown to be reversible and experimental studies suggest they are not reversible. The extent to which the neurobehavioural changes adversely influence the workers' quality of life and working ability cannot be easily defined. The changes observed could affect both parameters. In this context, neurobehavioural changes have the potential to enhance the susceptibility of the worker to the deleterious effects of environmental influences, particularly social influences. In the final analysis, the health significance of the neurobehavioural changes observed with lower levels of occupational lead exposure remains controversial. Given that they can be interpreted as adverse health effects would seem to argue for the exercise of caution when considering the potential health significance of these neurobehavioural changes.

TABLE 5-II

QUALITY EVALUATION QUESTIONS FOR STUDIES OF NEUROBEHAVIOURAL FUNCTION

1. Were the sample subjects representative of the population(s) from which they were drawn?

2. Was there a control group(s)?

3. Was there adequate matching of exposed and control groups for age and sex?

4. Was there control for socioeconomic status?

5. Was there control for education or intellectual level?

6. Was there complete separation of exposed and control groups on the body lead measure(s)?

7. Was blood lead measured at the time of testing?

8. Was there more than one blood lead measurement spaced over a period of time?

9. Was use made of respectable (reliable, valid) psychological methods?

10. Were psychological functions which were said to be investigated assessed in some depth?

11. Was a range of psychological functions investigated?

12. Was the assessment done "blind"?

13. Were appropriate statistical tests applied?

TABLE 5-III

TOTAL SCORES ON QUALITY EVALUATION QUESTIONS FOR STUDIES OF NEUROBEHAVIOURAL FUNCTION

Study		Total Score
Valciukas	et al. 1980 (37)	7.5
Arnvig	et al. 1980 (38)	4.5
Mantere	et al. 1982 (39)	8.5
Mantere	et al. 1984 (40)	8.5
Baker	et al. 1983 (41)	8.0
Baker	et al. 1984 (42)	10.0
Baker	et al. 1985 (43)	10.0
Hogstedt	et al. 1983 (44)	10.0
Campara	et al. 1984 (45)	11.0
Zimmerman-Tansella	et al. 1983 (46)	10.0
Parkinson	et al. 1986 (47)	11.5
Araki	et al. 1986 (48)	7.5
Williamson	et al. 1986 (49)	9.5

Maximum possible score 13.0

TABLE 5 - IV SUMMARY OF NEUROBEHAVIOURAL STUDIES

Study	Type	Mean PbB (Range) (ug/100 mL) Exposed	Control	Test Battery	Results	Evaluative Score (maximum 13.0)
Valciukas et al. 1980 (37)	cross-sectional	51.1 ± 12.0	—	WAIS	significant negative correlations of lead exposure indices (PbB, ZPP), with tests of visual learning, visuomotor and psychomotor performance.	7.5
Arnvig et al. 1980 (38)	cross-sectional	(58 - 82)	no control	WAIS Others	decreased attention, concentration, memory and psychomotor performance.	4.5
Mantere et al. 1982 (39)	prospective - start - TWA-PbB - 2 years	 15.3 ± 6.7 28 ± 7.9 30.5 ± 9.6	 10.5 ± 3.7 10.3 ± 4.0	WAIS SADT WMS Others	deterioration in visual intelligence, memory, visuomotor function and vigilance.	8.5
Mantere et al. 1984 (40)	prospective - 4 years	 28.8	 6.8	WAIS WMS SADT Others	no significant differences at 4 years.	8.5
Baker et al. 1983 (41)	cross-sectional	33.9 (8-80)	18.6 (3-36)	WAIS WMS POMS SADT Others	increased reported depression, confusion, anger, fatigue, tension and trouble remembering for PbB above 40 ug/100 mL. Impaired tests of abstract concept formation and memory for PbB above 40 ug/100 ml.	8.0
Baker et al. 1984 (42)	prospective	(13 - 80) (Combined Groups) [32.8(10 - 80)]	(10 - 42)	same as Baker (38)	multiple regression analysis showed significant negative correlation of current exposure level with performance tests of visual intelligence, memory and mood profiles. Cumulative exposure (TWA-PbB over 1 year) showed significant correlation with mood.	10.0

POMS = Profile of Mood States
TWA-PbB = Time-Weighted Average - Blood Lead Level
WMS = Wechsler Memory Scale
SADT = Santa Ana Dexterity Test
WAIS = Wechsler Adult Intelligence Scale

TABLE 5 - IV SUMMARY OF NEUROBEHAVIOURAL STUDIES (Continued)

Study	Type	Mean PbB (Range) (ug/100 mL) Exposed	Control	Test Battery	Results	Evaluative Score (maximum 13.0)
Baker et al. 1985 (43)	prospective	(23 - 50) all exposed means now <40 ug/100 mL	(8 - 31)	same as Baker (38)	multiple regression analysis showed significant associations between various current and cumulative lead exposure indices with mood scores, and measures of dexterity and learning.	10.0
Hogstedt et al. 1983 (44)	cross-sectional (retrospective exposure) - TWA-Pb - current PbB	47.7 (26.9-68.4) 41.4	< 20.7 14.5	Swedish Psychological Test Battery	significant differences in memory, learning and reaction time.	10.0
Campara et al. 1984 (45)	cross-sectional - high lead - low lead	52.2 ± 5.1 (46-60) 31.7 ± 2.9 (26-35)	20.4 ± 6 (11-27)	WAIS GHQ -30 SSQ-22 Others	significant differences in visual learning, verbal abstraction and comprehension, attention and psychometric function of high lead versus low lead and non-exposed. High lead reported significantly more symptoms. significant correlations of PbB with perceptual and psychomotor tests and verbal abstraction and comprehension.	11.0
Zimmerman-Tansella et al. 1983 (46)	cross-sectional - high lead - low lead	52.2 ± 5.1 (46-60) 31.7 ± 2.9 (26-35)	20.4 ± 6 (11-27)	GHQ-30 SSQ-22	significant difference in subjective psychological and physical symptoms for high lead compared to low lead and controls. signficant correlation of PbB levels with neurological and gastrointestinal symptoms but not psychological symptoms.	10.0

GHQ-30 = General Health Questionnaire
SSQ-22 = Subjective Symptom Questionnaire

TABLE 5 - IV SUMMARY OF NEUROBEHAVIOURAL STUDIES (Continued)

Study	Type	Mean PbB (Range) (ug/100 ml) Exposed	Control	Test Battery	Results	Evaluative Score (maximum 13.0)
Parkinson et al. 1986 (47)	cross-sectional -current -TWA-PbB	40.0 ± 13.2 48.8 ± 11.9	< 35	Psychosocial WAIS Others	similar psychosocial and neuropsychologic test results between groups. significant dose-response association with exposure and inter-personal conflict.	11.5
Araki et al. 1986 (48)	cross-sectional	42 (16-64)	13 (8-20)	WAIS (5 subtests)	significant difference in one psychometric subtest. significant correlation of PbB level with one psychometric subtest; significant correlation of this subtest with spinobulbar conduction time.	7.5
Williamson et al. 1986 (49)	cross-sectional	48.9 (24.7-81.2)	not done	Information Processing Performance Tests	significant differences in visual sensory, psychomotor and cognitive performance. multiple regression analysis revealed no significant relationships except for one memory test.	9.5

5.2.2 Neurophysiological Effects

Prior to 1980 the results of studies of peripheral nerve conduction velocities and their association with PbB level were inconsistent. In a number of studies nerve conduction velocities were found to decrease in association with lead exposure in the absence of overt neurological findings and some studies reported significant dose-response relationships. However, negative studies were also reported. Recent work concerning the association of nerve conduction velocity measurements and lead exposure indices will now be considered in greater detail.

Araki et al.[52] studied 14 Japanese male lead workers with initial PbB levels between 15 and 83 μg/100 mL. Motor nerve conduction velocities were measured after which the workers were treated with calcium disodium ethylene diaminetetraacetate (CaEDTA), a chelating agent which reduces the body lead burden. The authors reported improvement in motor conduction velocities over time and concluded that the alteration in motor conduction velocity was significantly negatively correlated with the concurrent change in PbB levels. Selection bias, small sample size, lack of adequate controls and the failure to address the potential confounding effects of several variables (e.g., independent treatment effect of CaEDTA) make definitive conclusions from this study impossible.

Ashby [53] compared 94 male lead workers (mean PbB level 60 μg/100 mL) to 94 unexposed matched controls and found a significant slowing of motor nerve conduction velocities in the exposed workers. The author was unable to demonstrate a significant dose-response relationship, i.e., that progressive slowing of nerve conduction was associated with increased exposure to lead as measured by blood and urine lead concentrations. There was only one nerve (ulnar) in which conduction velocity was significantly correlated with length of exposure to lead. A subgroup of workers exposed to lead for less than 2 years had significant reduction of

motor conduction velocities in several nerves. The PbB level of this subgroup was 58 μg/100 mL at the time of testing and had never risen above 80 μg/100 mL.

No significant independent correlations between lead exposure and nerve conduction measurements of velocity and latency were reported by Spivey et al. [54] in a study of smelter workers. The one significant difference in a motor nerve conduction velocity for exposed, compared to unexposed workers, was possibly related to age differences. A significant difference in the accuracy of eye movements was postulated as indicating evidence of a subclinical effect on the nervous system (mean exposed PbB level 60 - 66 μg/100 mL). No difference was found after comparing high versus low level lead-exposed workers although this may have been secondary to the choice of a relatively high PbB level (60 μg/100 mL) used to separate high from low levels of lead exposure.

In a cross-sectional study of 78 workers, Seppalainen et al.[55] found a statistically significant dose-effect relationship between the maximal PbB level ever measured and various measurements of median, ulnar and posterior tibial motor and sensory nerve conduction. Abnormal conduction velocities were found in 27% of workers with maximal PbB levels between 40 and 49 μg/100 mL whereas 53% of the workers had recorded abnormalities if their maximal PbB levels ever exceeded 70 μg/100 mL. Among workers whose maximal PbB level had exceeded 50-69 μg/100 mL, four nerve conduction velocities were significantly slower than those of a non-occupationally lead-exposed group. Seppalainen et al.[55] also reported on nerve conduction parameters in a prospective study of workers with neither previous lead exposure nor known occupational exposure to other neurotoxic chemicals. At the initial examination the exposed workers had a mean PbB level of 15.7 μg/100 mL. At the one and two year study points the mean PbB levels were 30.2 and 30.5 μg/100 mL respectively with 90% of the workers at both one and two years having levels below 45 μg/100 mL. The

lead-exposed group showed a tendency towards decreasing motor and sensory nerve conduction velocities of the upper extremities but the results were not statistically significant. If the exposed workers were split at 30 μg/100 mL, some significantly reduced conduction velocities were noted in the higher blood lead group. Difficulties which affect the interpretation of this work include the high loss to follow-up (30% of exposed men remained at one year and 21% at two years for the neurophysiological analysis) and the serious bias that could result from losing a disproportionate number of high blood lead workers from the study. Using the same data, the authors proposed under separate title [56] a non-effect PbB level for changes in nerve conduction velocities of 40 μg/100 mL. The choice of this level appears somewhat arbitrary given that the range of PbB levels was 30-48 μg/100 mL in those workers with slowed nerve conduction velocities. A further report [57] on 10 (11%) of the original number of eligible workers showed no significant differences in peripheral nerve conduction velocities at 4 years compared to the control group. Using an internal comparison within the exposed group, there was significant slowing of motor conduction velocity for only the median nerve at 4 years for workers with a median PbB level greater than or equal to 29 μg/100 mL. Those workers whose PbB level had risen quickly to over 30 μg/100 mL had a tendency to quit after one or two years and those workers who remained after four years had a slower initial rise in their PbB levels. This fact, in addition to a PbB level less than 30 μg/100 mL in six of the ten workers helps explain the four year follow-up results. The number of people studied and the loss to follow-up do not permit firm conclusions from this later follow-up. The absolute neurophysiological changes noted over the study period within the PbB range 30-50 μg/100 mL were mild with a slight actual decrease in conduction velocities.

An Italian cross-sectional survey by Bordo et al. [58] demonstrated significant alterations in nerve conduction

velocities and conduction latencies compared to a reference group for workers who never had mean PbB levels greater than 50 μg/100 mL in the two year period prior to examination and who had total lead exposure for less than 10 years. The authors reported several electrophysiological alterations to be more evident for workers with maximal PbB levels between 50-69 μg/100 mL and with an exposure time less than 2 years and less evident for subjects with a longer exposure time. Self-selection bias could have been the sole determinant of this outcome.

Nielsen et al. [59] found no difference in motor nerve conduction velocities for controls compared to workers exposed to lead for longer than 9 years. The range of PbB levels for the exposed group was wide (13 - 91 μg/100 mL) with a mean of 51 μg/100 mL compared to a mean PbB level of 10 μg/100 mL for the controls. Controls were not well matched with the exposed workers nor were sensory nerve conduction measurements taken. Worker self-selection over time may have also occurred.

In the Proceedings of an International Symposium on Neurobehavioural Methods in Occupational Health, Sborgia et al.[60] reported no significant differences in a survey of battery plant workers compared to iron foundry workers for several neurophysiological parameters including nerve conduction velocities. No consistent dose-effect relationship was reported although an analysis of variance was presented for only one motor nerve conduction velocity. The mean PbB level for lead-exposed workers was 62 ± 19 μg/100 mL and for the controls was 24 ± 7 μg/100 mL indicating that the controls were not truly unexposed. The controls were employed significantly longer than the exposed workers although there was no difference in age. This implies that self-selection may have been differentially operable between the exposed workers and the controls. This could decrease the magnitude of any differences in neurophysiological parameters between the two groups. The authors concluded that no single neurophysiological

parameter is adequate for the purposes of medical surveillance. They further suggested that inconsistencies between studies of neurophysiological parameters may be partially explainable on the basis of a recurring, remitting pattern of neurotoxicity similar to that found in demyelinating diseases. This hypothesis, in combination with individual susceptibility may explain some inconsistencies in the cross-sectional surveys.

Six additional cross-sectional studies [61,62,63,64,65,66] were all positive in some respect regarding the association of lead exposure and alterations in nerve conduction measurements. Rosen et al. [61] found small but significant correlations between lead exposure and motor and sensory nerve conduction velocities for workers with moderate lead exposure (high mean PbB levels approximately 40-55 μg/100 mL). Singer et al.[62] suggested that sensory nerve conduction velocity changes occur earlier than motor nerve conduction changes. Corsi et al.[63] examined workers who had not worked with lead for at least three years. During exposure their blood lead values ranged between 71-180 μg/100 mL but had decreased to a minimum of 27.9 μg/100 mL at the time of examination. Compared to controls not occupationally exposed to lead, significant nerve conduction velocity alterations were noted, although no correlation between dose and effect was found. The authors concluded that subclinical signs of neuropathy persist for some time after cessation of exposure. The relevance of this to more moderate levels of PbB is not clear. Triebig et al. [64] studied lead-exposed workers with a median PbB level of 53.2 μg/100 mL (range 22-90 μg/100 mL) and unexposed controls with PbB levels less than 20 μg/100 mL. Significant differences for the distal sensory conduction velocities of the ulnar and median nerves were found between the two groups. Significant differences were predominantly observed for exposed workers with time-weighted average PbB levels (TWA-PbB) greater than 70 μg/100 mL although these differences were not exclusive to that level. The authors noted a continuous percentage

increase of abnormal conduction velocities with increasing lead exposure, suggesting a dose-response relationship which also held for PbB levels below 70 μg/100 mL. Despite these findings, the authors concluded that statistically significant dose-response relationships may be assumed only for PbB levels above 70 μg/100 mL. They further concluded that no functionally significant lead-induced slowing of nerve conduction velocities is to be expected, even with chronic exposures at PbB levels below 70 μg/100 mL. This conclusion appears based not on the absence of observed significant changes but rather on a speculative judgement of what constitutes functional significance. Jeyaratnam et al.[65] examined workers exposed to a combination of organic and inorganic lead. The mean PbB level was 48.7 μg/100 mL. Significant changes were found in both nerve conduction velocities and somatosensory evoked potentials and distal latencies of the median and posterior tibial nerves. Chen et al. [66] found significant negative correlations of median nerve motor conduction velocity with PbB level and length of exposure to lead. A significant decrease in median nerve motor conduction compared to controls was found for lead-exposed workers with PbB levels less than 40 μg/100 mL, although the mean of this subgroup of workers was not specified and may have bordered closely on the upper limit of 40 μg/100 mL. These additional studies generally support other work demonstrating significant neurophysiological changes at low to moderate levels of lead exposure. Variations in the specific nerve affected can also be taken as demonstrating lack of consistency in the literature. Jeyaratnam et al. [65] postulated that this variation could result from a random rather than a selective effect of lead on peripheral nerves.

Most recently, Araki et al. [67] measured the distribution of conduction velocities in sensory fibres of the median nerve in 20 workers exposed to lead, zinc and copper and in 20 unexposed controls. Rather than restrict the analysis to slower or maximal nerve conduction velocities, the authors used a computerized analytical technique to study a full

range of conduction velocities. Mean PbB levels were 39 μg/100 mL and 13 μg/100 mL for the exposed and unexposed workers respectively with ranges of 22 - 59 μg/100 mL and 8 - 20 μg/100 mL respectively. Exposed workers had elevated plasma zinc and copper levels compared to controls. Compared to the control group, significant reduction of the maximal conduction velocity and a slower sensory nerve conduction velocity were found for those workers with PbB levels greater than 40 μg/100 mL. Three slower sensory conduction velocities were inversely correlated both with PbB level and with body lead burden as measured by a CaEDTA test administered to the exposed workers. Notably, various measurements of the sensory conduction velocities of the faster fibres were positively correlated with indicators of zinc absorption. The authors suggested that zinc may have antagonized the effects of lead on the fast nerve fibres and that the effects of zinc must be considered when conduction velocities are not decreased in lead-exposed workers. This latter point may have relevance when considering apparently inconsistent results in the literature. Small sample size, the possibility of sampling bias, worker self-selection and the failure to consider the possibility of previous severe lead intoxications weaken this study. However, it does augment the existing literature respecting a decrease in nerve conduction velocities in lead-exposed workers and raises the interesting question of the associated effects of zinc exposure which may be protective.

The majority of the literature on the neurophysiological effects of lead has dealt with peripheral nerve function. However, Cavalleri et al. [68] examined the effects of lead on the visual system of occupationally exposed subjects compared to matched unexposed controls. The mean PbB level for the exposed workers was 47 μg/100 mL (range 21-82 μg/100 mL) and 23 μg/100 mL (range 21-37 μg/100 mL) for the controls. A highly significant decrease in visual sensitivity was observed for the exposed workers, suggesting subclinical optic neuropathy. In addition, Glickman et al.[69] found a significant decrease in eye movement

accuracy during eye fixation from one point to another (saccadic eye movements) for lead-exposed workers (mean PbB level 56.6 μg/100 mL) compared to controls not lead-exposed (PbB levels not available). Decreased saccadic accuracy was also significantly correlated with PbB and ZPP levels. These results require replication but highlight the potential for lead exposure to affect various aspects of nervous system function.

In Summary: Although some inconsistency persists in the literature, the bulk of the evidence suggests that changes in peripheral neurophysiological function occur in association with PbB levels in the range 40-60 μg/100 mL. The literature is inconclusive as to the length of exposure required to produce the changes or whether there is reversibility of the noted effects.

Procedural differences and difficulties aside, inconsistent results are partially explained by individual susceptibility or biological variation. Although the absolute values of the neurophysiological parameters measured may often be considered in the "normal" range, statistically significant changes have been observed. Again the question of the clinical significance of these findings is perhaps the most difficult point to consider and reference to Appendix 2 as a guideline is made. Decrements in peripheral nerve function may be postulated as being an early subclinical stage of frank neuropathy, although this has not yet been established. The changes are not known to be either reversible or irreversible and it is not clear that they enhance individual susceptibility to other body stresses. Practical impairment of functional capacity has not been demonstrated but is possible. Adverse effects on peripheral nerves may play a partial role in producing the changes in psychomotor function previously described. The issue of the clinical significance of subclinical changes in the function of peripheral nerves is perhaps more controversial than that for neurobehavioural effects. Has the worker's ability or quality of life been affected? Are there potential long

term ramifications which may become manifest later in life? These questions remain unanswered.

Changes in peripheral nerve function occur with lead exposure in a dose-response fashion. Lead neuropathy is noted at higher lead exposure levels. Slowed nerve conduction velocities are found in frank neuropathy due to lead as well as in demyelinating diseases with peripheral neuropathy. Peripheral nerve dysfunction is perhaps more easily translated into an adverse health effect than is a more obscure metabolic effect several steps removed from a clinical endpoint. This in itself may lead some to consider detectable changes in peripheral nerve function as unacceptable.

As was done in the previous section, Tables 5-V and 5-VI list relevant evaluative questions and score the quality of the major studies examined and Table 5-VII summarizes the major relevant articles which were discussed in greater detail.

TABLE 5-V

QUALITY EVALUATION QUESTIONS FOR STUDIES OF NEUROPHYSIOLOGICAL FUNCTION

1. Were the sample subjects representative of the population(s) from which they were drawn?

2. Was there a control group(s)?

3. Was there adequate matching of exposed and control groups for age and sex?

4. Was there control for socioeconomic status and smoking?

5. Was there control for skin temperature?

6. Was there complete separation of exposed and control groups on the body lead measure(s)?

7. Was blood lead measured at the time of testing?

8. Was there more than one blood lead measurement spaced over a period of time?

9. Was use made of respectable (reliable, valid) physiological methods?

10. Was a range of physiological functions investigated?

11. Was the assessment done "blind"?

12. Were appropriate statistical tests applied?

TABLE 5-VI

TOTAL SCORES ON QUALITY EVALUATION QUESTIONS FOR STUDIES OF NEUROPHYSIOLOGICAL FUNCTION

Study		Total Score
Araki	et al. 1980 (52)	5.0
Ashby	1980 (53)	7.5
Spivey	et al. 1980 (54)	8.5
Seppalainen	et al. cross-sectional, 1980 (55)	8.5
Seppalainen	et al. prospective, 1980 (55)	8.0
Seppalainen	et al. 1982 (56)	8.0
Seppalainen	et al. 1983 (57)	8.0
Bordo	et al. 1982 (58)	6.0
Nielsen	et al. 1982 (59)	8.5
Sborgia	et al. 1983 (60)	8.5
Rosen	et al. 1983 (61)	4.0
Singer	et al. 1983 (62)	7.5
Corsi	et al. 1984 (63)	7.0
Triebig	et al. 1984 (64)	10.0
Jeyaratnam	et al. 1985 (65)	6.0
Chen	et al. 1985 (66)	6.0
Araki	et al. 1986 (67)	8.5

Maximum possible score 12.0

TABLE 5 - VII SUMMARY OF NEUROPHYSIOLOGICAL STUDIES *

Study	Type	Mean PbB (Range) (ug/100 mL) Exposed	Control	Exp vs Non-Exp Significant Differences of Nerve Conduction Velocities	Dose-Effect or Dose-Response of Nerve Conduction Velocities	Comments	Evaluative Score (Maximum 12.0)
Araki et al. 1980 (52)	prospective	47.7 (15-83) (median)	———	———	change of median MCV negatively correlated with individual change of PbB.	———	5.0
Ashby et al. 1980 (53)	cross-sectional	60 ± 15	24 ± 14	ulnar MCV median MCV radial MCV peroneal MCV	no consistent correlation of MMCV, SFCV with PbB; ulnar MMCV negatively correlated with length of lead exposure but positively correlated with PbB.	"... a subclinical neuropathy was present in the lead workers tested ..."	7.5
Spivey et al. 1980 (54)	prospective - initial - 1-1.5 years	 60.0 ± 11.9 66.2 ± 12.5	 22.1 ± 6.2 27.9 ± 8.4	ulnar MCV (questionable)	no significant independent correlations.	"nerve conduction measurements are probably not a good early indicator of lead effect on the nervous system."	8.5

MCV = motor conduction velocity
MMCV = maximal motor conduction velocity
MSCV = maximal sensory conduction velocity
SCV = sensory conduction velocity
SFCV = slow fibre motor conduction velocity

* adapted from Sborgia et al. (60)

TABLE 5 - VII SUMMARY OF NEUROPHYSIOLOGICAL STUDIES (continued)

Study	Type	Mean PbB (Range) ug/100 mL Exposed	Mean PbB (Range) ug/100 mL Control	Exp vs Non-Exp Significant Differences of Nerve Conduction Velocities	Dose-Effect or Dose-Response of Nerve Conduction Velocities	Comments	Evaluative Score (Maximum 12.0)
Seppalainen et al. 1980 (55)	cross-sectional - group 1 - group 2	21.2 ± 6.9 (lowest mean) 36.9 ± 8.11 (highest mean)	10.5 ± 3.5	several unspecified nerve conduction velocities	median SCV, median MCV, ulnar SFCV, ulnar SCV and posterial tibial MCV negatively correlated with max PbB.	"the slowing of nerve conduction velocities should be regarded as a warning sign of incipient neuropathy."	8.5
Seppalainen et al. 1980,1982 (55,56)	prospective - initial - 1 year - 2 year	15.7 (7-30) 30.2 (13-48) 30.5 (13-48)	10.5 (1-21) 10.5 (7-18) 10.3 (5-21)	no significant differences between exposed and non-exposed. - for internal controls (PbB > 30 ug/100 mL): median MCV at 2 years median SCV at 2 years	significant differences noted between lead-exposed workers separated by a PbB of 30 ug/100 mL.	"impairment in the function of the peripheral nerves is caused by very low lead exposure." non-effect level of 40 ug/100 mL for change in function of peripheral nerves.	8.0
Seppalainen et al. 1983 (57)	prospective - 4 years	27.2 (17-37)	6.9 (4-12)	no significant differences between exposed and controls at 4 years. for internal controls (PbB > 29 ug/100 mL): median MCV at 4 years.	———	"lead effects on peripheral nerves start at .... PbB >30 ug/100 mL."	8.0

TABLE 5 - VII SUMMARY OF NEUROPHYSIOLOGICAL STUDIES (continued)

Study	Type	Mean PbB (Range) (ug/100 mL) Exposed	Control	Exp vs Non-Exp Significant Differences of Nerve Conduction Velocities	Dose-Effect or Dose-Response of Nerve Conduction Velocities	Comments	Evaluative Score (Maximum 12.0)
Bordo et al. 1982 (58)	cross-sectional	< 50 for 2 years	15.8 ± 3.2	median MCV median SCV	no correlation with length of exposure; correlation with maximal PbB.	"electrophysiological changes occur whenever the PbB exceeds a threshold level (about 50 ug/100 mL)..."	6.0
Nielsen et al. 1982 (59)	cross-sectional	51 ± 2 (13-91)	10 ± 1(6-16)	no significant differences of three motor nerves	no significant correlations.	"subclinical neuropathy could not be detected even after long-term exposure...below... 70 ug/100 mL."	8.5
Sborgia et al. 1983 (60)	cross-sectional	62 ± 19	24 ± 7	no significant differences	no consistent dose-effect relationship.	"no single neuro-physiological parameter seems to be useful in the medical surveillance of low level lead exposed subjects..."	8.5
Triebig et al. 1984 (64)	cross-sectional	53.2 (22-90) (median)	< 20	ulnar distal SCV median distal SCV	multiple regression analyses revealed significant correlations with PbB; a significant dose-response relationship may be assumed for PbB levels > 70 ug/100 mL; study suggests dose-response relationship for PbB levels < 70 ug/100 mL.	"...below... 70 ug lead/dl blood in man, no functionally significant lead-induced slowing of the nerve conduction velocity is to be expected, even with chronic exposure."	10.0
Araki et al. 1986 (67)	cross-sectional	39 (22-59)	13(8-20)	median SCV (slow, fast fibres)	inverse correlation of slower median SCV with PbB and CaEDTA test.	"conduction velocities of slower fibres were inversely affected by lead ... significant reduction ... at the PbB level of 40-59 uq/dl."	8.5

5.3 Reproductive System

Since the preparation of the earlier health effects document, few additional articles respecting the direct effects of lead on human reproduction have been published. Effects on fertility and observable neonatal adverse health effects have not been widely studied. There is developing a related literature regarding the relationship between prenatal and perinatal lead exposure and subsequent child development which will be discussed in some detail below. In addition, recent animal experimental studies (post 1980) which are relevant will be reviewed.

5.3.1 Animal Studies

Recent reviews [70,71,72] of the reproductive toxicity of lead have noted that a large body of experimental data indicates that lead in relatively high doses is toxic to reproductive function in both male and female laboratory animals. Recent relevant experimental studies of animal (mammal) reproduction using low to moderate levels of lead exposure will now be considered.

Willems et al. [73] did not demonstrate changes in sperm count or morphology nor testis histology nor any observable cytogenetic effects in rabbits with PbB levels ranging from 6.6-61.5 μg/100 mL. In a study with low PbB levels, Wiebe et al. [74] concluded that lead exposure of the fetal rat prenatally by subcutaneous injection of mothers with lead and postnatally by ingestion of mother's milk significantly reduced testicular steroid production and hormone binding in the offspring. Lead concentrations in the blood of the lead-exposed offspring were only 6.3 μg/100 mL compared to 3.4 μg/100 mL in the control rat offspring. However, the mothers were treated with 40 mg/kg lead, a moderately high dose. There existed the possibility of lead being sequestered in tissue at the site of injection and therefore sporadic elevation of blood lead level could have occurred during the experiment due to intermittent release of lead

from the injection sites. The authors concluded that the metabolic aberrations observed might be expected to affect the onset of sexual maturation in the male by impeding the onset of gametogenesis. This conclusion is speculative. Sokol et al.[75] exposed male rats to lead in drinking water resulting in PbB levels of 60 and 34 μg/100 mL for 2 exposed groups and below detection level for a control group. Significant negative correlations were found between PbB level and serum testosterone, intratesticular testosterone and intratesticular sperm counts. Ancillary investigations on serum gonadotrophins led the authors to conclude that the predominant action of lead toxicity was through suppression of the hypothalamic-pituitary axis although a component of direct testicular toxicity could have also occurred. They further concluded that rats exposed to PbB levels at or below 40 μg/100 mL experienced inhibited testicular function. It should be noted that there were only 8 rats in each group. The clinical significance of the affected parameters was not assessed in terms of fertility nor, as occurs frequently, is it clear at which PbB level within the range investigated that a clinically significant adverse effect occurs. Sokol et al.[75] also reviewed other recent experimental research indicating published agreement and disagreement with aspects of their work. Chowdhury et al.[76] exposed male rats to a range of lead acetate concentrations in drinking water resulting in PbB levels of 54, 72 and 143 μg/100 mL and compared them to control rats with a PbB level of 9 μg/100 mL. Decreased testicular weight and cellular degeneration were noted in the high exposure group, and reduction of spermatid count and seminiferous tubular diameter in the group with PbB levels of 72 μg/100 mL. No significant changes were seen at the lower exposure levels.

In another experimental study of rats prenatally exposed to lead in drinking water and subsequently cross-fostered postnatally to mothers not lead-exposed, McCauley et al.[77] observed a significant delay in rat cerebral cortical development (as measured by the number of synapses/m^3 of

tissue) compared with rats not lead-exposed. No significant depression of synaptic counts was observed in pups exposed only during the postnatal period. The authors concluded that prenatal, not postnatal, lead exposure accounted for the delay in neurophysiological development. Rat pup PbB levels at birth were moderately high (mean PbB level 69.2 μg/100 mL) for the animals exposed to lead prenatally only.

Miller et al.[78] administered lead orally by gavage to rats before and during pregnancy. Maternal PbB levels during pregnancy ranged from 53 to 92 μg/100 mL. No significant teratogenic response was noted on gross and microscopic examinations for the lead-exposed fetal rats at the 20th day of gestation although a significant reduction in conceptus weight occurred for the group with maternal PbB levels during pregnancy of 92 μg/100 mL. Hayashi [79] administered relatively low doses of lead orally in drinking water to pregnant rats starting at the beginning of gestation. He found no significant occurrence of prenatal fetal mortality or external fetal malformations but did demonstrate a significant decrease in fetal weight for the offspring of lead-exposed dams. The dose of lead administered was so low that the control versus lead-exposed dams had similar PbB levels (approximately 4 μg/100 mL) but the lead-exposed group did have significantly higher liver lead levels. Fetal PbB levels were similar for lead-exposed rats versus controls at day 18 of gestation but were significantly higher at day 21 for the lead-exposed fetuses (18 μg/100 mL). Wardell et al. [80] exposed pregnant rats to lead by gavage for a range of lead concentrations (10 mg/kg/day (low) to 150 mg/kg/day (high)) and found significantly decreased prenatal fetal survival for the high exposure group. No evidence of internal or external fetal malformations was noted.

Additional studies [81,82] on rats and mice have demonstrated increased prenatal fetal mortality, smaller litter size, occurrence of fetal malformations and decreased

fetal birthweight, although the lead was administered to the pregnant dams intravenously and not by ingestion or inhalational exposure, the normal routes of environmental exposure. Wide [83] observed small litters and increased numbers of fetal deaths among progeny of female mice which were previously exposed to lead in utero. The initial lead exposure was as lead chloride given intravenously on day 8 of pregnancy which resulted in quite high post-injection PbB levels. Wide [83] suggested that the observed fertility decrease was due to failure of some female germ cells to develop into ovarian primordial follicles.

Carpenter [84] investigated nutritional aspects of lead-exposed hamsters. It was found that combining exposure of female hamsters to leaded drinking water prior to and/or during pregnancy with diets deficient in calcium or iron markedly increased their blood lead levels over lead-exposed females fed normal diets. The incidence of embryonic/fetal mortality and of abnormal fetuses was markedly increased in calcium and iron-deprived, lead-exposed animals compared with lead-exposed control animals. The author concluded that the critical threshold concentration of lead in maternal blood in hamsters for the development of teratogenic effects appeared to be between 100-150 μg/100 mL.

In Summary: Animal studies have indicated adverse effects of lead on adult reproductive function and offspring. The majority of the evidence has been in relatively high lead exposure situations. Sufficient low lead exposure studies with consistent results have not yet been done from which reliable dose-response models can be derived for lower levels of lead exposure. Even if this information existed or becomes available, extrapolation of such animal data to humans is always controversial. Variable biological susceptibility and differences in embryonic growth rates, gestational period and placental structure and function are examples of factors which hamper inter-species comparisons. The animal studies suggest that there exists the potential for effects on human reproduction at lower lead exposures and help set the stage for further definitive investigation.

5.3.2 Human Studies

5.3.2.1 Male Reproductive Function

As was the case with the experimental data discussed previously, studies in man attempting to relate low dose lead exposure and male reproductive function have been scarce. The most relevant earlier study in man which demonstrated an effect on lead at moderate (mean PbB level 53 μg/mL) to high (mean PbB level 75 μg/mL) levels of exposure was reported by Lancranjan et al. and was discussed in some detail in the previous health effects document[1]. Design weaknesses and the possiblity of measurement error made the results of this study inconclusive.

More recently Wildt et al. [85] studied two groups of men occupationally exposed to lead. The PbB levels ranged from 25-75 μg/100 mL in one group and 8-39 μg/100 mL in the comparison group. The high PbB level group tended to have decreased prostatic function, as measured by seminal plasma constituents and lower semen volumes. Meaningful statistical significance of these results was not demonstrated. Some individuals in the lower PbB level group actually had lower measurements for live and motile sperm compared to the high PbB level group. The results were seriously confounded by a differing frequency of urinary tract infections between the two groups. A true non-exposed matched control group was not studied and the actual effects on fertility were not evaluated. Butrimovitz et al. [86] found no relationship between seminal lead and sperm count or motility in a group of men with low semen lead concentrations (4 μg/100 mL).

In a study of 7 lead-intoxicated workers with a mean PbB level of 73 μg/100 mL and a range of maximum PbB level from 66 to 139 μg/100 mL, Cullen et al [87] found 5 workers with a defect in spermatogenesis. Subsequent to an endocrine evaluation of the exposed workers, the authors postulated both a central hypothalamic-pituitary-testicular effect of

lead exposure as well as an end-organ testicular effect. The literature, including the Cullen et al. [87] study on the reproductive effects associated with the exposure of human males to lead was recently critically reviewed by Uzych [88]. He concluded that data pertaining to teratogenesis and mutagenesis associated with the exposure of human male to lead is relatively meager and incomplete with conflicting published results.

In Summary: The recent literature remains inconclusive respecting the effects of chronic low dose lead exposure on male reproductive function and adequate dose-response relationships cannot be formulated.

5.3.2.2 Female Reproductive Function

Historically, relatively high levels of lead exposure have been associated with adverse reproductive effects in women, particularly involving spontaneous abortions and stillbirths. Recently Saric [89] studied the spontaneous abortion and twinning rate in a lead-exposed community near a lead smelter compared to a control region. Blood lead levels were not measured although air lead levels in the exposed community averaged approximately 20 $\mu g/m^3$. Saric [89] demonstrated a decrease in the twinning rate and an increase in the rate of spontaneous abortions in the exposed community. Although lead exposure was suggested as a possible cause, the study design does not definitely support this conclusion as the association with lead may have been indirect and the observed results due to other differences in the communities studied. The paucity of recent research on the effects of low dose lead exposure on the occurrence of stillbirths or abortions particularly in an occupational setting is probably largely explained by the frequent exclusion of pregnant women from lead exposure.

No new information was found concerning the direct effects on female fertility of chronic low dose lead exposure. Effects on women with respect to reproductive outcome will

be further considered from the perspective of teratogencity and also in particular from the perspective of the adverse effects on the embryo/fetus/newborn in association with prenatal and perinatal lead exposure.

5.3.2.3 Teratogenesis

Recent literature on the teratogenic effect of lead in humans has been scant and the teratogenic effect of chronic low dose lead exposure in humans remains unclear. Needleman et al. [90] analyzed the lead content of umbilical cord blood of over 5000 newborns. A logistic regression model was used to control for demographic and socioeconomic confounders. Cord blood lead level was found to be associated in a dose-related fashion with an increased risk for minor congenital anomalies. Such anomalies included hemangiomas ("birth marks") and lymphangiomas (masses of lymphatic vessels), hydroceles (fluid collections in association with the testicles), skin tags and undescended testicles. The relative risk for the occurrence of a malformation was estimated to increase by 50% when lead levels were increased from 0.7 μg/100 mL to a mean value of 6.3 μg/100 mL and an additional 50% when lead levels increased to 24 μg/100 mL. No specific malformation was associated with lead. The authors suggested that lead may interact with other teratogenic risk factors to enhance the probability of an abnormal outcome. Diagnostic assessment of anomalies was carried out by pediatric resident physicians and not specialists in teratology and therefore misclassification errors may have occurred. Stillbirth data was not examined nor was race nor past history of anomalous pregnancy outcome. Birth weight and gestational age were not related to lead exposure. The hospital from which the sample was taken was a referral center for high risk pregnancies. Although an attempt was made to control for other confounding factors, this select sample population lessens the relevance of the study to the general fertile female population.

McMichael et al. [91] have recently reported some initial results of an Australian prospective study as discussed in greater detail in Section 5.3.2.6. No association of perinatal PbB level and congenital anomalies was observed for low level lead exposure.

5.3.2.4 Chromosomal Damage

Numerous studies and reviews of the association of lead with chromosomal aberrations have yielded contradictory results in workers exposed to lead [71,92,93,94,95,96,97,98]. Lead added to human peripheral lymphocytes does cause *in vitro* increased sister chromatid exchange (SCE) rates although PbB levels have not been shown to correlate *in vitro* with either chromosomal aberrations or SCE rates. Smoking is associated with an increased rate of SCE, and smokers who are lead-exposed have significantly higher SCE rates than smokers not lead-exposed. The clinical significance of SCE and chromosomal aberration potential is uncertain.

5.3.2.5 Placental Transport of Lead

Baltrop [99] has demonstrated that lead can be detected in the fetus at twelve weeks of gestation and that fetal tissue lead concentration increases throughout development. Neonatal umbilical cord PbB levels correlate positively with maternal PbB levels and are similar to, or perhaps slightly less than, the maternal PbB level. Khera et al.[100] found an increase in the placental lead content in women with increasing length of occupational exposure to lead. Alexander et al. [101] have shown a decrease in maternal PbB level during pregnancy in women not occupationally lead-exposed even after accounting for the effects of hemodilution associated with pregnancy. The authors postulated that this could be secondary to an increased transfer of lead to the placenta and/or fetus during pregnancy or possibly due to an increased loss of body lead such as by excretion in the urine. A similar trend was observed by Bonithon-Kopp et al.[102] although their results

fell just short of clinical significance ($p<.07$). Ong et al.[103] have demonstrated a greater affinity of fetal hemoglobin for lead although the significance of this is not clear.

A critical question concerns the placental transport of lead in the first trimester. Borella et al. [104] studied the lead content in abortion material from urban women in early pregnancy. They found no correlation of maternal PbB level with lead content of abortion material. The authors concluded that in their population lead does not accumulate in human fetuses in the first trimester. The women studied were not occupationally exposed and had mean PbB levels of 11 μg/100 mL. Although low levels of lead were detected in abortion material in the first trimester, the authors inferred that this originated in maternal not fetal tissue. It cannot be concluded with certainty that lead does not cross the placenta in the first trimester of occupationally lead-exposed female workers.

5.3.2.6 Prenatal and Perinatal Lead Exposure

In the occupational setting, the effects of lead exposure on the embryo/fetus of a female worker must be considered. Studies which have examined the relationship between human embryonic or fetal lead exposures and subsequent developmental outcomes are rare. Cases of prenatal lead intoxication have been reported in the literature (e.g., 105). The lead exposure of the surviving fetus has not been directly measured except by umbilical cord blood lead measurements at birth. A number of different centers are investigating the effects of community prenatal and perinatal lead exposure on subsequent child development. Although not involving workers occupationally exposed to lead, these studies will be reviewed in some detail because of their potential relevance to the occupational setting. The emphasis will be placed on studies involving some measure of fetal lead exposure rather than an attempt to review all the pediatric lead-related literature. The

effect of lead on the fetus is of particular relevance to occupational regulatory considerations.

Bellinger et al. [106] performed a longitudinal study on a group of infants and classified lead exposure by umbilical cord blood measurements. No cord PbB levels were greater than 30 μg/100 mL. The authors reported that high cord PbB levels (mean 14.6 μg/100 mL) were associated with lower covariance-adjusted scores at 6 months of age on a standardized Mental Development Index (MDI) of the Bayley Scales of Infant Development. However, they did not find a significant association with high cord PbB level using a standardized Psychomotor Development Index. PbB levels taken at 6 months of age were not found to be associated with either of these indices of development. The authors concluded that their data were compatible with the hypothesis that low levels of lead delivered transplacentally are toxic to infants. No significant association of cord PbB levels with birth weight or gestational age was noted, although the exclusion from the study of infants from pregnancies less than 34 weeks of age could have underestimated the association of PbB levels with shortened gestational period. Bellinger et al.[107] recently updated their prospective study by performing follow-up assessments at 12 months of age and found infants' umbilical cord PbB level to be significantly related to MDI scores taken at 12 months. Infant PbB levels taken at 6 or 12 months of age were not significantly associated with adjusted MDI scores taken at 6 or 12 months of age. The authors concluded that the deficit observed in MDI scores for infants with umbilical cord PbB levels greater than 10 μg/100 mL (mean 14.6 μg/100 mL) at age 6 months persisted until age 12 months. Additional analyses suggested that fine motor and interactional/linguistic skills were the behavioural parameters most strongly related to prenatal lead exposure. Control for numerous confounders through a multivariate analysis was done. Sampling technique was targeted towards middle to upper class infants thus limiting the external validity of the study to the population at

large. The design of this prospective study is generally sound and included an evaluation of ascertainment bias. However, the absolute changes observed in the developmental indices, although statistically significant, may have resulted from small or fractional changes in the raw scores from which the indices are derived. Indeed the scores of infants in the high prenatal exposure group were above the mean of Bayley's standard sample. This is perhaps not surprising considering the target sample. However, a significant difference in behaviour was observed for infants with cord PbB levels greater than 10 μg/100 mL. The psychological significance of these differences is unclear and makes it difficult to clarify the impact of low level fetal lead exposures on subsequent neurological development. Regardless, Bellinger et al.[107] concluded that the high exposure infants were less capable partners in their early social transactions.

In Cincinnati, Bornschein et al. [108] are conducting a prospective study of the effects of chronic, low level lead exposure on a cohort of children. Maternal PbB levels were done at recruitment and umbilical cord PbB levels were taken at birth as a measure of fetal lead exposure. Infant PbB levels were also taken at 10 days of age and every three months thereafter. The cohort was recruited from particular medical and social backgrounds and was at high risk for lead exposure. The group was thus chosen as being at the greatest risk for adverse developmental effects of low level lead exposure. The intent of this choice was to remove the potential "protective" influences of better health and higher socioeconomic status on subsequent development. Standard psychometric measures of infant development are being used to assess outcome (e.g., Bayley Scales of Infant Development). Mean maternal prenatal and umbilical cord PbB levels were less than 10 μg/100 mL. Initial results as reported by Dietrich [109] do not generally support the hypothesis that postnatal exposure to lead at these levels results in a delay of early sensorimotor development. Postnatally, 3 month PbB levels were associated with delayed

development as measured at 6 months but the result was no longer significant when adjusted for birth weight and home environment. Padich et al. [110] studied a subsample of infants from the Cincinnati Prospective Study who had reached the age of 18 months by July 1984. A battery of behavioural tests were used to measure attention span. No significant association was found between lead exposure and the infant's ability to maintain attention. Mean maternal prenatal PbB level was 7.9 μg/100 mL and mean infant 18 month PbB level was 16.8 μg/100 mL. The authors felt that no infants evidenced activity levels or patterns of attention clinically consistent with a diagnosis of attention deficit disorder with hyperactivity. A weak negative association was actually found between activity level and PbB level, a finding of questionable significance but which may suggest more active children come into greater contact with lead in their environment. The authors attempted to control for parental caretaking behaviour in a multivariate analysis. Scoring of infant behaviour was done blindly with good interscorer reliability. The Cincinnati group has a well-designed ongoing prospective study which must be closely monitored for further results.

In Scotland, Moore et al. [111] measured mental and motor development outcomes at one and two years of age using the maternal first trimester PbB level as an index of fetal lead exposure. Preliminary results as reported by Starr [112] have revealed no relationship between maternal PbB level and early behavioural development as measured by the Bayley Scales. The ranges of blood lead levels included high (PbB level greater than 30 μg/100 mL), intermediate (PbB level 10-30 μg/100 mL), and low (PbB level less than 10 μg/100 mL) exposure groups. It was postulated that biological and social variables may interact with fetal lead exposure to enhance any adverse health effects measured. Although the exposure groups were matched for social variables, the authors did not analyze the effects of any interaction between lead exposure and these other variables. Further reporting from Moore et al. [111] on this cohort is expected.

Moore et al. [113] separately reported a significant negative correlation for length of gestation versus maternal and cord PbB levels in a cross-sectional survey of 236 mothers and infants lead-exposed through drinking water. Mean maternal and cord PbB levels were 23 and 17 μg/100 mL respectively in the 11 cases of pre-term delivery. Birth weight was not found to vary significantly with perinatal PbB levels.

Winneke et al. [114] analyzed 114 six to seven year old children in Germany, using both umbilical cord blood and maternal blood PbB levels as measures of fetal lead exposure. The mean cord PbB level was 8.2 μg/100 mL with a range of 4-31 μg/100 mL. Maternal PbB levels taken at delivery ranged from 4 - 30 μg/100 mL with a mean of 9.3 μg/100 mL. Present PbB levels for the children ranged from 3.9-22.8 μg/100 mL with a mean of 8.2 μg/100 mL. A step-wise regression analysis was used to control for confounders including social and medical factors and pica. Outcome measures included standard tests of psychological performances (e.g., Wechsler Intelligence Scale for Children), some of which were scored by a separate German scoring system. For intelligence and visuomotor integrative functions no association was found with cord PbB level or maternal PbB level. A slight but significant negative association of performance with PbB level at 6-7 years was found but no association between visuomotor integration and present PbB level was found. A significant reaction performance deficit was associated with present and maternal PbB level but not cord PbB level. In general, the authors found the degree of association to be stronger for present PbB level rather than for perinatal PbB level. The outcome of the study suggested that lead exposure later in childhood has a somewhat stronger impact on neuropsychological development than perinatal levels. This conclusion remains speculative when one considers maternal PbB levels taken at delivery were noted to have some influence on subsequent development and that 70% of eligible children were not followed.

Vimpani et al. [115] are conducting another prospective study in Port Pirie, Australia. Both maternal and cord PbB levels were measured. Initial results as reported by McMichael et al. [91] have demonstrated a significant association, in a dose-response manner of pre-term delivery with maternal PbB level taken at delivery. Compared with women having PbB levels of 8 μg/100 mL or less, women with PbB levels of 9-11 or 12-14 μg/100 mL at delivery had 2.1 and 3.0 times the risk respectively, while those women with a mean PbB level of 17.1 μg/100 mL were found to have a 4.4-fold increase in the risk of pre-term delivery as determined by gestational age. The latter group was the only group with a statistically significant relative risk estimate. Mean umbilical cord PbB levels were 12.7 μg/100 mL for the infants of pre-term pregnancies as determined by gestational age and 12.2 μg/100 mL for the infants of pre-term pregnancies as determined by neonatal assessment. No association with PbB level was detected for 5 other outcomes of pregnancy, namely spontaneous abortion, low birth weight, intrauterine growth retardation, premature rupture of membranes and congenital anomalies. Multiple logistic regression analyses did not demonstrate social status or occupation to be related to the relative risk of pre-term delivery. However, the accuracy of using husband's occupation as the determinant of social status may be questioned. Also, first measurements of maternal PbB levels were taken at 14-20 weeks of gestation so that any possible effects of earlier higher PbB levels on fetal development would not have been taken into account. Postnatal follow-up is ongoing and involves measurement of PbB levels and various indices of development.

Ernhart et al. [116] attempted to identify maternal life-style variables which correlated with fetal lead exposure. Maternal PbB levels taken at delivery ranged from 3.0 to 11.8 μg/100 mL with a mean of 6.4 μg/100 mL and infant cord PbB levels ranged from 2.6 to 14.7 μg/100 mL with a mean of 5.7 μg/100 mL. Maternal or infant PbB levels were not related to alcohol abuse but alcohol use during pregnancy

was related in a dose-response fashion to both these measures of PbB. Both maternal and infant PbB levels were also related strongly to maternal smoking. Maternal smoking and drinking in pregnancy were estimated to account for 10.6% and 7.8% respectively of the variance in maternal and cord PbB levels. Preliminary results are available and as reported by Starr [112] indicated that 4 of 17 neonatal outcome measures were significantly related to perinatal lead levels (two positively and two negatively), although the outcome variable most highly related to lead (abnormal reflexes) was not significantly related after accounting for the associated variables of smoking and blood hematocrit level. A more detailed, final report of this prospective study is necessary, including an assessment of developmental outcomes at later stages of infancy and childhood.

Similar prospective studies are underway in at least three other centers. Data collection is ongoing and numerous publications are expected during the remainder of the decade.

Bonithon-Kopp et al. [116] have recently examined hair lead levels of newborns and their relationship to psychomotor development six years later. The mothers were not reported to be knowingly lead-exposed during pregnancy. A significant negative correlation was found between a child's perceptual performance scores and motor scores on the McCarthy Scales of Children's Abilities at six years of age compared with hair lead levels at birth although no significant correlation was found for general cognitive, verbal or memory scores. Small sample size, potentially biased sample selection and the possible influence of intervening variable lead exposure and differential socioeconomic status at the time of testing weaken this study. Controversy also surrounds the use of hair lead levels as a valid and reliable measurement of lead exposure. Regardless, the study does reinforce the concern that prenatal lead exposure is of consequence to later psychomotor development.

In Summary: With respect to the effects of prenatal lead exposure, the prospective human studies of prenatal and perinatal exposure to lead have produced variable results and have on occasion been questioned with respect to aspects of study design and clinical significance of measurement outcomes. Other considerations such as biological, socio-economic and environmental factors also impact on the outcome of pregnancy and make association of a specific factor (e.g., Pb exposure) with outcome a difficult and complex issue.

Maternal lead levels have been measured at various times during pregnancy and have generally reflected measures of fetal, not embryonic lead exposure. However, since exposure of the embryo to lead is likely to have preceded exposure of the fetus to lead, it is not possible to relate any of the postulated effects of prenatal lead exposure to early effects on the embryo or later effects on the fetus. Therefore in the final recommendation respecting the effects of prenatal lead exposure, the term conceptus is used to cover all periods of human prenatal development. Noteably, fetal estimates of lead exposure were generally less than 30 μg/100 mL with means of approximately 8-10 μg/100 mL. These mean values are much less than that expected in an occupational setting. Low level fetal lead exposure has not been clearly associated with the occurrence of congenital anomalies or low birth weight. Similarly, the association of reduced gestational age with low level lead exposure of the fetus has not been consistent although recent work by McMichael et al. [91] is more convincing. Although additional reporting is expected for several ongoing prospective studies of the association between fetal lead exposure and neurological development, the studies alert us to the potential for adverse neurological effects in children due to prenatal and perinatal lead exposure at very low lead levels. One could reasonably expect this potential for adverse neurological effects to be exacerbated in the occupational setting where lead exposures are generally higher.

Lead is a reproductive toxin in sufficient dose. However, dose-response relationships have not been formulated from the experimental literature. Direct effects on both male and female human reproductive organs have not been clearly demonstrated at low levels of lead exposure. Low dose lead exposure has not been demonstrated to be teratogenic. The literature is inconclusive respecting the mutagenic effects of lead in humans with respect to their occurrence as well as their clinical significance. Low birth weight and shortened gestational age may be associated with low level fetal lead exposure but the literature is not consistent nor conclusive regarding these two outcomes. Neurological fetotoxicity of very low doses of lead has been suggested but dose-response relationships remain undefined.

Because of its limitations, current knowledge regarding most aspects of the reproductive toxicity of lower doses of lead exposure cannot play a direct role in the setting of occupational standards. Rather the critical question relative to reproductive function appears to be the permissible exposure of the conceptus to lead in the workplace. Lead crosses the human placenta and neonatal umbilical cord PbB levels correlate positively with and are similar to maternal PbB levels. For practical purposes, limiting the blood lead level in the conceptus requires a similar limitation in the pregnant female.

5.4 Renal System

Occupational lead nephropathy has been recognized in association with frank lead poisoning. More recent work on the renal effects of chronic lead exposure in non-overtly toxic subjects will now be examined. Investigators have often attempted to correlate the results of various laboratory diagnostic tests with lead nephropathy.

In a study of 140 workers, Wedeen et al. [118] noted that the PbB level was of little value in predicting either an elevated lead-mobilization test (a measure of body lead

burden) or lead nephropathy. At least 15 men with lead nephropathy were identified and had PbB levels ranging from 20-98 μg/100 mL with a mean of 51.7 μg/100 mL. The minimal incidence of occupational lead nephropathy in asymptomatic workers with PbB concentrations less than 80 μg/100 mL and excessive body lead burdens as evidenced by CaEDTA lead-mobilization levels greater than 1000 μg lead per day was crudely estimated at 16%. Improvement in renal function as measured by the glomerular filtration rate (GFR) was noted subsequent to decreased body lead burden by a CaEDTA mobilization of body lead stores, suggesting causality and reversibility of lead-induced renal dysfunction. The majority of workers had not been lead-exposed for one year prior to testing, thus diminishing the usefulness of PbB measurements. The study was not controlled and the independent renal effects of the CaEDTA treatment were not clear. The results were further jeopardized by the high drop-out rate of those found to have a high body lead burden and whose renal function was never tested.

Chelation therapy with CaEDTA in very high doses above the usual therapeutic dose may be associated with renal damage in the form of tubular necrosis. On occasion in the past, chelation with CaEDTA was advocated to maintain low PbB levels in lead-exposed workers. The use of prophylactic oral CaEDTA therapy over the long-term may be associated with increased lead absorption from the gastrointestinal tract and depletion of body stores of certain trace metals. Furthermore, it is not clear whether CaEDTA over the long term may be associated with direct renal effects or the progression of pre-existing renal disease. As demonstrated by Hryhorczuk et al. [5], a reduction in the PbB levels caused by short-term chelation may be short-lived since lead is mobilized from body lead stores, particularly bone. Prophylactic CaEDTA treatment to maintain low PbB levels is therefore not without possible side-effects and is an unacceptable substitute for safe working conditions and good work practice.

Lilis et al. [119] investigated renal function in two groups of lead-exposed workers. They did not observe an association between PbB levels and renal function as measured by elevation of blood urea nitrogen (BUN) nor did they observe a consistent association between PbB levels and serum creatinine, another measure of renal function. In only one group of workers was there a correlation between PbB levels and serum creatinine. Significant correlations of zinc protoporphyrin levels with BUN and creatinine levels and duration of lead exposure with BUN and creatinine levels were observed. The correlation with duration of exposure persisted after controlling for the age-dependent effect on renal function. Chelation therapy had been used in the past in both groups although in one group only 19% of the lead-exposed workers reported ever having received chelation therapy, compared to 45% of the other group of exposed workers. Independent confounding effects of CaEDTA therapy on renal function are therefore possible, although less so in one worker group. Blood lead levels ranged widely in both groups, from less than 40 μg/100 mL to greater than 80 μg/100 mL. In addition, the time course of lead exposure was not known and PbB levels could have been very high in earlier years of exposure. Despite the absence of consistent correlations of serum creatinine with PbB levels and the recognition of BUN as a poor indicator of renal function because of its inherent variability, the authors concluded that the correlations with zinc protoporphyrin levels confirmed the etiologic relationship between lead exposure and impairment of renal function. They further concluded that chronic exposure to lead resulting in PbB levels above 60 μg/100 mL posed a definite risk of renal impairment.

Hong et al. [120] investigated six adults with occupational exposure to lead with PbB values ranging from 34 - 110 μg/100 mL. They found that routine clinical laboratory tests (e.g., BUN, serum creatinine) were insensitive for the detection of early renal effects but that measurement of renal tubular absorptive capacity of

glucose (TmG) was a sensitive measurement. The clinical significance of this defect is unknown.

Buchet et al. [121] found no evidence of kidney dysfunction among 25 lead-exposed workers whose PbB concentrations averaged 44 μg/100 mL with an upper limit of 62 μg/100 mL. Two problems with their study were that the control groups were not truly unexposed and the length of exposure varied from 3.1 to 29.8 years.

Batuman et al. [122] examined the role of lead in gout nephropathy. The authors noted that excessive lead exposure had been previously associated with gout. They investigated 44 men with gout, 22 of whom had impaired renal function. No subjects had a history of lead poisoning or were currently exposed but 26 gave a history of either industrial lead exposure or "moonshine" whiskey consumption, a potential source of lead exposure. The mean PbB level was 26 μg/100 mL for renally impaired patients and 24 μg/100 mL for patients not renally impaired. There was a significant increase in body lead burden as measured by CaEDTA lead mobilization values for patients with gout and renal failure compared with patients with gout who had normal renal function. The severity of renal disease correlated directly with the mobilizable lead burden. Controls with a similar degree of renal dysfunction but without gout had normal body lead stores as measured by the CaEDTA test. This indicated that the excessive body lead burden was not a consequence of decreased renal function. The authors suggested that lead plays an etiologic role in the nephropathy found in gout. Wright et al. [123] did not find elevated chelatable lead in 7 of 10 patients with gout, hypertension and mild to moderate renal insufficiency but did find elevated chelatable lead in the remaining 3 patients, all of whom had a history of lead exposure. This study suggested that factors other than lead may be the cause of renal failure in patients with gout but does not exclude lead as an etiologic agent for renal failure in other patients. Recently, Behringer et al [124] studied the body lead burden as

measured by the CaEDTA test of patients with impaired renal function both with and without gout. Elevated body lead burden was found in 7 of 8 patients who developed gout in the course of renal failure of known cause, but the PbB level was elevated in only 2 of 8 patients with gout prior to the development of renal failure. Mean PbB levels for patients with impaired renal function prior to gout was 18.5 μg/100 mL and for patients with gout prior to impaired renal function was 10.3 μg/100 mL. In contrast to the findings of Batuman et al. [122], a number of patients with renal failure of known cause but without gout had elevated body lead burdens. This may have been solely due to a difference in past history of lead exposure. Behringer et al. [124] suggest that it is unlikely that past lead exposure is an important cause of renal failure in patients with gout but that the appearance of gout in patients with impaired renal function is a strong indication of past lead exposure. Considering the small sample size and the absence of adequate statistical analyses, these conclusions remain hypothetical.

Campbell et al. [125] investigated the effects of renal function on lead kinetics. Thirteen patients with normal renal function and 27 patients with impaired renal function were studied. They found that renal failure did not affect PbB concentration or renal lead clearance. A highly significant inverse correlation between PbB concentration and renal lead clearance was noted. Two subjects with PbB concentrations greater than 41 μg/100 mL had marked renal impairment. The authors interpreted their findings as evidence of sub-clinical lead-induced nephrotoxicity.

Meyer et al. [126] utilized another sensitive indicator of renal injury, urinary acetyl glucosaminidase activity, to evaluate workers exposed to lead. Compared to controls, exposed workers had significant increases in this enzyme activity as measured in the urine. The enzyme changes were not correlated with either PbB levels or ZPP levels. It was noted that all five persons with PbB levels greater than

70 μg/100 mL had normal enzyme excretion whereas abnormal enzyme excretion was found in workers with PbB levels between 40-70 μg/100 mL. Whether the renal effects noted are harmful or innocuous is unknown.

Recently, Greenberg et al. [22] found "few significant renal abnormalities" in an uncontrolled study of 38 workers with mixed exposure to lead and cadmium. Lead exposures may have been high in the past but current mean PbB levels were 32 μg/100 mL. The renal abnormalities noted were abnormal BUN and uric acid levels and abnormal urinary protein β_2 microglobulin excretion, the latter a specific protein indicative of renal tubular dysfunction. Impaired urinary concentrating ability was also observed. The clinical significance of these subclinical findings is not clear; a more reliable measure of renal function, creatinine clearance was not affected. An independent effect of lead could not be separated out in this cross-sectional survey.

In Conclusion: It is seen that lead exposure is related to the development of nephropathy and that lead may be causally related to urate nephropathy. A threshold level of blood lead for renal impairment has not been adequately defined and PbB concentration has not been consistently correlated with renal function. Duration of exposure to lead has been associated with renal impairment although the exact nature of this relationship is unknown. Reversibility of lead induced renal effects is a possibility and is a current area of research. The recent literature reviewed suggests that a PbB level in the range 50-60 μg/100 mL maintained over time may be too high to protect workers from eventually developing clinically apparent kidney dysfunction. Levels of PbB below this range may be related to subclinical nephrotoxicity, the significance of which remains unclear.

5.5 Hypertension

Research dealing with the cardiovascular effects of chronic exposure to lead has largely considered the association of

lead with hypertension. As this subject has not been discussed in the earlier health effects document [1] and given that it has become a particular area of interest, the literature prior to and subsequent to 1980 will be assessed.

An early occupational health study which raised the suspicion that lead exposure might be associated with cardiovascular disease was a mortality study by Dingwall-Fordyce et al. [127] This study concluded that heavy exposure to lead was associated with an increased incidence of death from cerebrovascular causes with which hypertension may be associated.

Cramer et al. [128] reported no greater association of hypertension with lead workers than with the general population. This study suffered from several methodological problems, namely the absence of a true unexposed control group, a questionable definition of exposure (positive urinary coproporphyrin at any time during employment) and failure to take precautions against biased or unreliable observations of blood pressure. In a subsequent similar study, Malcolm [129] found no significant degree of correlation between hypertension and lead exposure. This study was also uncontrolled and as a measure of exposure used the product of the concentration of lead in air and duration of exposure. This latter estimate of exposure does not account for individual workers' body lead burdens. In the preceeding two negative studies, confounders such as alcohol use and smoking habits, both known to potentially affect body lead burden were not considered. Such oversights and difficulties bring the negative conclusions of these studies into question.

A positive association of hypertension and blood lead was reported by Beattie et al. [130] in a community exposed to lead through drinking water. However, no useful statistical analysis could be applied because of the small number of persons with hypertension. The study was not controlled and potentially suffered from volunteer bias. In a non-

occupational study Beevers et al. [131] found a significant difference between PbB level in hypertensives versus normotensives. Mean PbB levels for hypertensive men and women were 27.1 and 22.3 μg/100 mL respectively and for normotensive men and women were 23.6 and 19.5 μg/100 mL respectively. However, no correlation was found between blood pressure level and PbB level. Controlling only for age and sex could allow confounding to occur with respect to several other variables. Cadmium-induced nephropathy and/or hypertension may have been a significant factor in this study.

Rogan et al. [132] studied the association of blood pressure and PbB levels in a small group of black children in North Carolina. PbB levels ranged from 7-66 μg/100 mL with a mean of 24.3 μg/100 mL. They found small but statistically significant negative correlations between blood pressure and PbB levels. The population studied was not a representative sample and a strict data collection protocol was not followed. Bias, unreliable data and lack of external validity weaken this study. Jhaveri et al. [133] reported that PbB concentrations greater than 40 μg/100 mL were associated with blood pressure elevations in infants and young children. The study was well controlled but did not demonstrate any significant dose-response relationships. In addition, 85% of the children studied were black, thereby limiting any generalizability of this study to other populations. In an attempt to relate body lead burden to hypertension, Friedlander et al. [134] found no significant relationship between blood pressure and a parameter referred to as the lead "mobilization ratio area" in children. This "area" was generated by integrating the duration of lead burden with the amount of lead mobilized by a single dose of penicillamine (a chelating agent) in children previously treated for lead poisoning. The PbB level was not found to be a significant contributor to the variations observed in blood pressure or creatinine clearance, a measure of renal function. However, there is a lack of comparability of duration and intensity of exposure

to lead in children versus adults industrially exposed. A child's physiological response to a body lead burden may differ significantly from the response in an adult.

Batuman et al. [135] used the CaEDTA lead mobilization test as an indicator of excessive body stores of lead in a well controlled clinical trial. Patients who had essential hypertension with reduced renal function had significantly larger amounts of mobilizable lead than did patients who had hypertension without renal impairment. Excess mobilizable lead was also significantly more frequent in essential hypertensives with renal impairment than in controls with renal impairment of known cause. The authors concluded that occult lead absorption contributed to both essential hypertension and renal insufficiency. The mean PbB values were similar for essential hypertensives without renal disease and for essential hypertensives with renal disease (18 ± 2, 19 ± 4 μg/100 mL respectively). To exclude renal impairment as a cause of excessive body lead burden they demonstrated no significant difference between lead excretion during the CaEDTA test in a group of normotensives with an equivalent amount of renal impairment.

Up to this point, it can be seen that the epidemiological studies have been inconsistent, often poorly designed and certainly somewhat confusing regarding the association of PbB level and blood pressure.

In a more recent cross-sectional study, Pocock et al. [136] found very small, close to zero, positive correlation coefficients between PbB level and systolic and diastolic blood pressures. Although the coefficient for PbB level and systolic blood pressure was statistically significant, the authors suggested that its very small value made it biologically insignificant. They also found a non-significant positive trend towards increased systolic and diastolic blood pressure in men with PbB levels greater than 37.3 μg/100 mL. The subjects were randomly selected from representative general medical practices in Great Britain.

Of 7735 middle aged men recruited, only 74 or 1% had a PbB level greater than 37.3 μg/100 mL. The authors concluded that no overall evidence was found associating PbB levels with the level of systolic or diastolic blood pressure. They further concluded that exposure to lead made a negligible contribution to high blood pressure in the general male population of Great Britain.

Sparrow et al. [137] reported no association between lead concentrations in drinking water and elevations in either systolic or diastolic blood pressure. No estimation of PbB level or body lead burden was made, making these results difficult to interpret. In a randomized sample survey, Staessen et al. [138] demonstrated that the level of urinary excretion of lead of Belgian townsfolk did not significantly contribute to blood pressure variability in a multivariate analysis. The utility of 24 hour urinary lead excretion as a valid measure of past lead exposure can be questioned.

Using uni- and multivariate regression analyses, Kromhout et al. [139] reported a significant correlation between PbB level and blood pressure in a cohort of 152 men aged 57-76 years with a mean PbB level of 18.3 μg/100 mL. After excluding one outlying value, the correlation between PbB level and systolic pressure was marginally significant and the correlation between PbB and diastolic pressure became insignificant. The effect of PbB level on systolic blood pressure was also not independent of other variables.

Orssaud et al. [140] in 1985 reported significant associations of PbB level with blood pressure in policemen aged 24-44 years but not for those aged 45-55 years. PbB levels were less than 37 μg/100 mL in 99% of the subjects studied.

Using data from the second National Health and Nutrition Examination Survey (NHANES-II) conducted in the United States between 1976 and 1980, Harlan et al. [141] found significantly higher PbB levels in men and women aged 21 to

55 years with hypertension. They noted that PbB levels were positively correlated with systolic and diastolic blood pressure for both sexes aged 12 to 74 years, although PbB levels were not found to be significantly different for any blood pressure categories in persons aged 56 to 74. Statistically significant results were found at mean PbB levels less than 20 μg/100 mL. This analysis found the relationship of PbB level to blood pressure to be independent of other variables in men but not in women after adjusting for more than 30 variables in a multivariate analysis. The failure to reach significance for older age groups might indicate the possibility of an age-dependent physiological response to lead as found by Orssaud et al. [140] Given that the data was collected in a cross-sectional survey rather than in a prospective analysis, inferences of causality may not be made with confidence.

Pirkle et al. [142] analyzed the same NHANES-II data as Harlan et al. [141] in a rigorous multivariate analysis utilizing 87 variables. An independent statistically significant relationship was found between systolic and diastolic blood pressure and PbB level. They limited their study to white males aged 40-59 years. No evidence of a threshold PbB level was found. The authors took the analysis one significant step further by predicting the impact of a decrease in PbB level on hypertension and cardiovascular mortality and morbidity. They concluded that the 37% decrease in mean PbB levels from 1976 to 1980 in the United States resulted in 1.3 million fewer white males aged 40-59 with hypertension. Subsequent impressive decreases in cardiovascular mortality and morbidity were postulated. These final analyses made the major unproven assumption of causality. The authors speculated with respect to the apparently inconsistent epidemiological studies of the effect of lead on blood pressure by raising the question of a biphasic response, i.e., the physiologic effects of lower PbB levels may differ from the effects at higher levels or after longer exposures. Pirkle's analyses took painstaking efforts to avoid confounding of the relationship between

blood lead and hypertension. Such efforts have not been taken in a occupational setting.

In a recent occupational study, Kirkby et al. [143] performed a retrospective analysis using well-matched controls. Mean PbB level in lead-exposed workers was 51 μg/100 mL and in controls was 11 μg/100 mL. A significant difference was demonstrated between lead-exposed cases and controls with respect to diastolic blood pressure but a significant correlation of blood pressure level with PbB level or zinc protoporphyrin levels was not found. The lead-exposed workers had significantly more ischemic electrocardiographic changes than the unexposed group and high-density lipoprotein cholesterol was significantly lower in the lead workers. These findings could indicate a higher risk for major cardiovascular disease among lead workers. The lack of correlation between blood pressure and PbB levels was felt to indicate that no causal relationship exists between these two variables, although the authors concluded that the study supported a positive association between lead exposure and arteriosclerosis and high blood pressure. The influence of the potential confounding effect of other occupational pollutants was not assessed.

The Cooper et al. [144] mortality study of lead battery plant and lead production plant workers represents an update of previously reported mortality analyses covering the period 1947 to 1980. Standardized mortality ratios (SMR) for all causes were significantly greater in both worker cohorts examined. The International Classification of Diseases (ICD-7) category "other hypertensive disease" includes deaths recorded as secondary to benign or malignant hypertension. For battery plant workers in this category a significantly elevated SMR of 320 was found. For this cohort the SMR for vascular lesions of the central nervous system (including stroke) was 93 and for all diseases of the circulatory system was 100. In lead production workers, the SMR for other hypertensive diseases was 475 (significant), for vascular lesions of the CNS was 132 (non-significant),

and for all diseases of the circulatory system was 91. Age and cause-specific death rates for white males in the United States as a whole were used in the generation of the SMR values. As race was not commonly noted on personnel records, SMR values were not calculated with race taken into account. Although the validity of the SMR analyses can be questioned on this basis, the authors concluded that the racial difference in age-adjusted death rates could not account for the excess in total deaths noted based on estimated proportions of non-white workers. It should also be noted that there was no way of estimating actual lead exposures except in those workers subject to biological monitoring. Cooper et al. [144] remarked that it was not desirable to limit analyses of deaths to those with monitoring data due to the fact that most monitoring information was post 1960 and did not accurately reflect earlier individual exposures. The monitored values did show that much of the population under study had been exposed to relatively high amounts of lead in comparison to current standards.

Weiss et al. [145] performed a longitudinal study on a cohort of 89 policemen over a period of 5 years. Using multivariate analytic techniques, a statistically significant association was found between PbB levels greater than 30 μg/100 mL and elevation of systolic pressure. No significant association was found for diastolic blood pressures. Mean systolic blood pressure in year 2 of the study was 122 mm Hg and in year 5 was 129 mm Hg. These levels are not considered to represent clinically elevated systolic blood pressures. The lack of association of lead with diastolic pressure remains unexplained and frustrates the interpretation of these results in relation to the diagnosis of hypertension.

Hypertension is a disease of multifactorial etiology and whose pathogenesis is not fully understood. It is therefore not suprising that attempts to relate any single factor such as lead exposure to the development of hypertension should

prove difficult and that inconsistencies or unexplained observations should be found.

The effects of lead on blood pressure are postulated to be mediated through its effect on the regulatory renin-angiotensin system. This system affects both vascular reactivity and adrenal aldosterone secretion, a hormone involved in salt retention. Plasma renin is a renal hormone ultimately involved in the production of a polypeptide, angiotensin II which is closely linked to the regulation of blood pressure. The mechanisms of lead's interaction with these biochemical/physiological processes in animals and man are areas of active research.

It is useful at this point to consider some of the recent experimental animal evidence respecting lead exposure and blood pressure. Kopp et al. [146] found significant elevations of systolic blood pressure at 3, 9 and 15 months in rats fed 5 ppm Pb in drinking water. However, no significant difference with controls was found at 6, 12 and 18 months. Aviv et al. [147] exposed rats to 1% lead acetate solution orally for 6 weeks (at 3-9 weeks of age) resulting in an initial mean PbB level of 155.0 μg/100 mL which decreased to 23.5 μg/100 mL at 25 weeks of age. A significant rise in systolic blood pressure was observed at 25 weeks of age compared to 12 weeks of age. Revis et al. [148] fed pigeons 0.8 ppm Pb in water and found significantly higher levels of diastolic blood pressure and atherosclerosis than found in pigeons fed calcium in water. Victery et al. [149] noted a significant increase in systolic blood pressure in rats exposed to a lead concentration in drinking water of 100 ppm beginning *in utero* until six months of age. The mean PbB level was 40.4 ± 1.4 μg/100 mL. This group also had decreased plasma renin activity. Animals drinking a lead concentration of 500 ppm and having a mean PbB level of 70.8 ± 1.8 μg/100 mL did not have blood pressures significantly different from controls and did not have decreased plasma renin activity. No significant differences in blood pressure for female rats

was found. In another lead-feeding study Victery et al. [150] reported that rats with PbB levels of 5.6 and 18.2 μg/100 mL did not develop hypertension but did have decreased plasma renin activity. Subsequently, Victery et al. [151] noted elevated plasma renin activity in rats lead-exposed during gestation until one month of age at which time their mean PbB levels were 30-70 μg/100 mL.

The experimental studies reviewed indicate a variable effect of lead on blood pressure in animals. Although the research can be interpreted as inconsistent, an alternate explanation is that the studies support the occurrence of a biphasic dose-response relationhip as previously suggested in humans by Pirkle et al. [142]

In a study of lead exposure and the renin-angiotensin-aldosterone system in man, Campbell et al. [152] found significantly positive exponential relationships between PbB level and plasma renin activity, angiotensin I, angiotensin converting enzyme and blood aldosterone levels. The mean PbB level was 35.6 μg/100 mL in the 33 normotensive subjects, of whom 25 were occupationally exposed to lead. This data generally supports the postulated mediation of the effect of lead on blood pressure in man via the renin-angiotensin-aldosterone system.

In Conclusion: The information respecting the association between hypertension and inorganic lead has been inconsistent although recent rigorous epidemiological analyses have been more consistent. Where found, a positive association has often not been specific nor consistently strong. A dose-response relationship has not been clearly outlined although a biphasic relationship has been postulated. The exact nature of this biphasic response requires further clarification in both animals and man. A causal relationship between lead exposure and hypertension is possible but has not yet been established. Although reasonable concern exists respecting the association of lead exposure and hypertension, an adverse impact of lead on the

blood pressure of occupationally exposed workers cannot yet be adequately defined.

5.6 Carcinogenesis

Baker et al. [153] and Lilis [154] have reported two case studies of renal cancer patients who had been occupationally exposed to lead. No causal connection can be made on this basis.

The International Agency for Research on Cancer (IARC) reviewed the evidence for the carcinogenicity of lead and lead compounds [155]. IARC concluded that inadequate evidence exists to conclude that lead or lead compounds are carcinogenic in humans and that the evidence is inadequate or unavailable regarding metallic lead or organolead compounds being carcinogenic to animals. IARC did conclude that sufficient evidence is available to indicate that certain lead salts (lead acetate, lead subacetate and lead phosphate) are carcinogenic in experimental animals. IARC noted that although some soluble lead salts have been shown to be carcinogenic to experimental animals, humans are exposed primarily to metallic lead and lead oxide. Kazantizis [156] also reviewed the evidence available and concluded that it is unlikely that humans are at risk of cancer due to lead exposure.

In an early report of his mortality study series, Cooper et al. [157] reported the standardized mortality ratio (SMR) for all malignant neoplasms to be marginally elevated at the 5% level of confidence in smelter workers but not significantly elevated for battery plant workers. Slight excesses but no significant elevations for gastrointestinal and lung tumors were noted. No excesses of renal cancer were found. Kang et al. [158] re-analyzed the Cooper et al.[157] cohort study data and found that cancer of the respiratory system and cancer of the digestive organs and of the peritoneum occurred in statistically significant excess among lead smelter workers as well as battery plant

workers. However, the re-analysis wrongly assumed a computational error by Cooper et al. [157] and used a one-tailed test of significance. If a two-tailed test is applied, the difference disappears for cancer of the respiratory system for lead smelter workers and for cancer of the digestive organs and peritoneum for battery plant workers. Therefore the hypothesis that lead is not carcinogenic to humans remains viable.

As discussed in Section 5.7, Cooper et al. [144] updated their mortality study on the cohort of battery and smelter workers. A significantly elevated SMR occurred for malignant neoplasms for battery workers, and a slight non-significant excess was noted in the smelter workers. The excess cancer deaths noted were predominantly of the gastrointestinal tract and lung. Concerning specific cancers, only the SMR for lung cancer in battery workers was marginally significant. Although the SMR for all gastrointestinal cancer was not significant, battery workers did have a significant elevation of the SMR for gastric cancer within the gastrointestinal classification. This was not found for the smelter workers. Excess renal cancer was not found. The serious potential confounding effects of smoking history, multiple exposures (e.g., chromate exposure) and geographic, ethnic and dietary factors and the lack of reliably documented exposure histories make reliable conclusions respecting the carcinogenesis of lead in man impossible from these mortality analyses.

5.7 Mortality

Prior to 1975, the mortality studies of Dingwall-Fordyce et al. [127] and Cooper et al. [157] were prominent in the literature. The former found no evidence of an increased death rate due to malignant disease, however they found that heavy exposure to lead was associated with an increased incidence of death from cerebrovascular accidents. As stated in the previous section, Cooper et al. [157] initially found a significantly elevated SMR for malignant

neoplasms in smelter workers but not in battery workers. No excess of deaths was found from stroke or hypertensive heart disease. Deaths classified as "other hypertensive disease" and chronic and unspecified nephritis were higher than expected at a borderline level of significance, but actual numbers of deaths were small.

An extension until 1980 of the Cooper et al. [157] mortality study was published in 1985 [144]. This time the authors found that mortality from all causes combined was significantly greater than expected in both cohorts, the SMR being 107 for battery workers and 113 for smelter workers. In battery plants, the significant excess deaths were reflected in elevated SMRs for malignant neoplasms, other hypertensive disease (mainly renal), chronic or unspecified nephritis and ill-defined conditions. In smelters, significant excess deaths were found for malignant neoplasms, other hypertensive disease, hypertensive heart disease, chronic or unspecified nephritis, ill-defined conditions and external causes such as suicides and accidents. There was no subdivision of the worker population by exposure and the cohort extended historically through years of heavy exposure followed by years of reduced exposure. Being unable to establish actual exposures of the cohorts and being unable to separate out possible confounding exposures to other substances, the authors could not relate the epidemiological findings to risk estimates for chronic lead exposure.

McMichael et al. [159] followed 241 male smelter workers in Australia diagnosed as having had lead poisoning during 1928-1959, of whom 140 were known to have subsequently died. Their cause of death profile was compared to that of 695 male workers not lead-exposed. Prior to 1965, the age-standardized proportional mortality analyses showed a significant excess of deaths from chronic renal disease and cerebral hemorrhage. In more recent years, these differences largely disappeared.

Malcolm et al. [160] studied 1,898 pensioners from lead acid battery factories who worked during the years 1925-1976. Exposure to lead was defined as absent, low or high. In those most highly exposed, cerebrovascular deaths occurred in significant excess among retirees aged 65-69 but not in workers dying during employment. There was also a significant excess of deaths from renal disease among retirees in the low and high exposure groups. It was noted that subsequent to 1985, the causes of most of the deaths from renal disease were not associated with nephritis or nephrosis but rather were subsequent to an infectious process assumed to be less directly associated with lead exposure. The low exposure group had a mean PbB level of 57 μg/100 mL in 1965-66, leading the authors to conclude that exposure to lead resulting in mean PbB levels of 57 μg/100 mL (5.2% exceeded 80 μg/100 mL) had not resulted in any excess of cancer, renal cancer, cardiovascular or hypertensive disease.

Selevan and co-workers [161] reported on the mortality of lead smelter workers in Idaho, many of whom had also been hard-rock miners. A cohort of 1,987 white males employed between 1940 and 1965 was assembled and causes of deaths were ascertained until 1977. Occupational exposures to lead and to other metals (cadmium, zinc, arsenic) were estimated from job titles only and most lead exposure had exceeded current industrial hygiene standards. Overall mortality was similar in the cohort to that of the United States male population. A non-significant excess mortality (SMR = 192) from chronic renal disease was found for the entire cohort although a significant excess was found for greater than 20 years of lead exposure or for a latency interval of over 20 years suggesting a positive dose-response relationship. A significant mortality excess for non-malignant respiratory disease was noted. Mortality from cerebrovascular or hypertensive vascular disease was not elevated nor was overall mortality from cancer, although a non-significant excess of renal cancer was noted, an observation which requires cautious interpretation. Cadmium exposure may have

had adverse renal effects. In an attempt to control for the possible confounding effects of past exposure to cadmium, the authors examined a sub-group of high lead/low other metal exposures and found similar trends in the SMR values as was evidenced in the entire cohort.

In Conclusion: An excess of cerebrovascular deaths among lead-exposed workers may have occurred in the past but is no longer consistently evident. Association of lead exposure with deaths from cancer has not been consistent; any observed excess may or may not represent a causal effect of lead. Excesses of deaths within the ICD category titled "other hypertensive disease" have been noted as well as deaths from chronic renal disease, the latter a fairly consistent finding among recent studies. These studies covered periods of variable, generally decreasing lead exposure which was commonly not documented. They confirm the potential vulnerability of certain organ systems to lead exposure, alert us to the necessity for documentation of exposures and indicate the need for adequate control of confounding factors in future studies. Further relevance of these mortality analysis to current occupational exposures can be questioned and reliable dose-response inferences may not be made.

5.8 Immune System

The effects of lead on the human immune system have not been widely studied. An early study by Reigart et al. [162] found no differences between a control group and a lead-exposed group of children (mean PbB level 45.3 μg/100 mL, range 41-51 μg/100 mL) with respect to complement levels, immunoglobulin levels and immune anamnestic response to tetanus toxoid antigen. Sachs [163] noted prolongation of diarrhea in three children with elevated PbB levels and who had shigellosis, a gastrointestinal infection. Ewers et al. [164] examined the immune function of lead-exposed workers with a mean PbB level of 51.4 μg/100 mL. A significant reduction in serum IgM was noted in the lead-exposed group

compared to controls (mean PbB level 11.6 μg/100 mL) and non-significant reductions in IgG, IgA and serum complement were also noted. A significant negative correlation was noted between PbB level and serum complement (C_3) and IgG level in the exposed and unexposed groups. Serum IgA levels and PbB level were significantly positively correlated in the exposed workers. Salivary IgA levels were significantly lower in the lead-exposed workers although no significant correlations with PbB level were evident. A slight tendency toward an increased frequency of colds and influenza infections in the lead-exposed workers was found.

The ability of lead to increase the susceptibility of animals to endotoxins and to impair the ability of an animal to combat infectious agents has been documented. Koller [165] has recently published an extensive review of the experimental animal evidence involving the effects of lead on the immune system. Low dose lead exposure appears to be related to antibody-mediated (humoral) and cell-mediated immunosuppression. Lead also suppresses macrophage-dependent immune responses in animals. Certain aspects of the animal data have been confusing and the actual mechanisms by which lead affects immune function remain unknown.

In Conclusion: Current knowledge is inadequate to define the effects of lead on the immune system of man. The literature at present does not support the formulation of a dose-response relationship which would be useful to determine permissable exposure limits. Additional experimental research and epidemiological studies must be conducted to determine whether lead alters immune function in man and whether these alterations, if they occur, are detrimental to health.

5.9 Endocrine System

An effect of lead on hepatic cytochrome P-450 containing mixed function oxidase systems has been alluded to (Section

5.1.2) previously. Similar enzyme systems are found in many human organs with endocrine functions including, for example the testes, ovaries and adrenals. Saenger et al. [23] demonstrated alterations of steroid metabolism in lead-exposed children. The occurrence and significance of lead on endocrine function in man remain largely unstudied at low to moderate levels of lead exposure.

Respecting thyroid function, a cross-sectional study of 47 men from a small brass foundry led Robins et al. [166] to conclude that a substantial inverse relationship between PbB level and serum thyroxine (T4) and estimated free T4 (EFT) levels existed in lead-exposed workers. The PbB level ranged widely (44-117 μg/100 mL) with a mean of 70 μg/100 mL. Other metal exposures included copper, tin and zinc. Refowitz [167] tried to duplicate the results using a random sample of male employees at a medium size secondary copper smelter. No observed relationship between free T4 and PbB level was noted and recalculation of the Robins et al. [166] data, excluding two "outliers", produced a slope similar to Refowitz's data. Refowitz concluded that there is no evidence that indices of thyroid function are adversely affected by long-term moderate blood lead elevations. In lead-intoxicated workers with a mean PbB level of 73 μg/100 mL, Cullen et al. [87] found abnormalities of thyroid function tests in 3 out of 7 workers. The authors postulated a central pituitary effect on the thyroid endocrine system. The effect of lower doses of lead exposure were not studied.

In Conclusion: The literature is inconclusive respecting the effects of low to moderate lead exposure on thyroid function. The effects of chronic low level lead exposures on other endocrine functions remain undetermined.

5.10 Clinical Symptomatology

Medical researchers have attempted to relate PbB levels and the occurrence of clinical symptoms in workers exposed to lead.

Baker et al. [28] examined the dose-response relationship between PbB level and the occurrence of symptoms in workers subjected to higher lead exposures and others exposed chronically to lower doses of lead. In the former workers, there was a positive association between the prevalence of clinical findings and PbB levels over 40 μg/100 mL. In the latter group, no such correlation was found. There was no external unexposed control group. Evidence of clinical lead toxicity (extensor muscle weakness and gastrointestinal symptoms) and biochemical toxicity (anemia) was found in workers with PbB levels in the range 40-79 μg/100 mL. No toxicity was reported at PbB levels below 40 μg/100 mL.

Hanninen et al. [168] found a significant excess of symptoms in lead-exposed workers whose PbB levels were never known to have exceeded 70 μg/100 mL compared to a non-exposed group. The symptoms studied related to the gastro-intestinal, psychological and neurological systems. Workers with PbB levels less than 50 μg/100 mL also had significantly more reported symptoms compared to controls, although less than the number of symptoms reported by the higher lead exposure group.

As part of a larger ongoing prospective study of the neurological effects of lead exposure, Spivey et al. [169] found significant differences of symptoms between workers with a mean PbB level of 61.3 μg/100 mL and controls with a mean PbB level of 22.0 μg/100 mL. The majority of differences were for central nervous system symptoms and muscle or joint pain. The authors found weak correlations between symptom reporting and indices of lead absorption which they felt indicated that factors other than lead absorption may be important in symptom reporting.

In a cross-sectional survey, Fischbein et al. [170] examined two groups of lead-exposed workers (mean PbB levels 27.7 μg/100 mL and 36.5 μg/100 mL) and found that despite the rare occurrence of clinically overt lead poisoning among the workers, 27% of the group with lower mean PbB levels and

37% with higher mean PbB levels reported central nervous system and/or gastrointestinal symptoms. There was no significant association between PbB level and reported symptoms but zinc protoporphyrin level was correlated with reported symptoms.

Cullen et al. [171] described 31 new cases of lead toxicity. They commented that in their experience, findings of lead toxicity are rare in patients with PbB levels which have never exceeded 40 μg/100 mL. They also reviewed the literature and concluded in association with their data that at PbB levels above 40 μg/100 mL, whole blood lead levels correlate positively with the number of complaints, extent of organ system involvement and severity of manifestations.

Williams et al. [172] administered the Cornell Medical Index health questionnaire to 81% of workers in a factory making lead acid batteries. PbB level and erythrocyte protoporphyrin (EPP) were known for almost all workers. There was a significant difference in "potentially lead-induced" symptoms between men with PbB levels at 60 μg/100 mL compared with those below that level. There was however a significant difference of dermatological and psychological symptoms reported between these two groups that could not be explained by lead toxicity. The investigators took this as an indication of the occurrence of reporting bias, making it difficult to reliably conclude that the excess of symptoms in the more highly exposed group was due to lead exposure.

Neri et al. [173] measured PbB levels in 245 Canadian lead smelter employees and their wives and compared them with 144 controls. An internal check for validity of reporting suggested that reporting bias was not excessive. Symptoms referable to lead toxicity were 2.2 times more likely to be found in men with a PbB level between 50-59 μg/100 mL than in men with levels less than 30 μg/100 mL. Five complaints accounted for over 50% of the excess symptoms reported: insomnia, weakness of arms/legs, heartburn-indigestion,

shakiness, and pain in bones/joints. "Days off work ill" were also related to PbB level and 70% of absenteeism in the plant was estimated to be "attributable" to the presence of a PbB level greater than 30 μg/100 mL. The authors concluded that application of more stringent exposure standards could bring about a worthwhile reduction in sickness absence.

Kirkby et al. [174] studied the prevalence of lead-induced subjective symptoms (headache, tiredness, nervousness, weight loss, abdominal discomfort) in 96 Danish lead workers (mean PbB level 51 μg/100 mL , 70% of workers less than 60 μg/100 mL) and 96 unexposed controls (mean PbB level 11 μg/100 mL). Their results indicated that subjective symptoms were "useless" as indicators of incipient lead poisoning. The controls had more tiredness, nervousness and almost as much abdominal colic as the lead workers. As with other similar cross-sectional studies, the healthy worker effect and reporting bias may have been operational.

In a recent report, Wang et al. [175] found significant differences between lead-exposed workers with a mean PbB level of 61.9 μg/100 mL (± 33.1 μg/100 mL) and unexposed workers with a mean PbB level of 18.5 μg/100 mL (± 12 μg/100 mL) with respect to reported symptoms referable to the central and autonomic nervous systems, digestive system and musculoskeletal system. In addition, reported symptoms referable to these same systems were positively and significantly correlated with PbB levels. Although medical interview methodology was poorly outlined and rather wide ranges of PbB levels were reported in both groups, this study lends additional consistency to the literature respecting the reported symptoms of lead-exposed workers.

In Conclusion: The studies reviewed suggest that symptoms of lead toxicity occur in workers below PbB levels of 80 μg/100 mL and as low as 40-60 μg/100 mL. The dose-response relationship is imperfect, particularly in relation to PbB level although it may be better for blood ZPP level.

The studies highlight the inadequate validity and reliability of using reported symptoms as a predictor of PbB level. It has been suggested that disability days are related to PbB level but this finding requires replication in more controlled circumstances. Workers' subjective reports may be biased by their knowledge of the adverse effects of lead. In short, the occurrence of clinical symptomatology confirms the possibility of organ dysfunction at lower levels of lead exposure but is inadequate alone as a measure of lead exposure.

6. Air Lead - Blood Lead Relationship

The Ontario Regulation respecting Lead made under the Occupational Health and Safety Act currently stipulates that the time-weighted average exposure of a worker to airborne lead, except tetraethyl lead, shall not exceed 0.15 mg/m^3 of air, and in the case of exposure to tetraethyl lead 0.10 mg/m^3 of air (Appendix 1). If changes in the medical code are proposed, it follows that the regulated exposure levels must also be re-examined. In this light, the air lead-blood lead relationship will now be discussed.

The relationship between PbB level and air lead (PbA) exposure is not linear over the entire range of possible exposures although there are subsets of exposure ranges for which a linear model serves as a functional approximation. An equation which describes a linear PbA-PbB relationship is:

$$PbB = \alpha + \beta PbA$$

α = intercept of PbB on PbA

β = slope of the line which describes the change in PbB for a unit change in PbA.

The PbA-PbB relationship has been evaluated for both adults and children and for community/environmental and occupational exposures. For the occupational setting, the slope of the PbA versus PbB relationship has been shown to

be considerably less than the slope for lower exposures as found in the community. This means that for a given decrease in PbA level at higher exposure levels, the relative decrease in PbB is predicted to be considerably less than at lower exposure levels. The PbA-PbB relationship becomes complicated at occupational exposure levels because of the difficulty in evaluating the influence of body lead pools other than blood and because PbB level is determined by a number of other variables apart from PbA level such as workers' hygiene habits and the nature of the work being performed.

The literature on the PbA-PbB relationship has been extensively analyzed, critiqued and summarized by several authors [176-181]. For community exposures at PbA levels much less than occupational exposures, the range in the literature for β is 0.1-3.09 $\mu g/100$ mL per $\mu g/m^3$ [70] although a value for adults in these situations is often approximated at 1.0 $\mu g/100$ mL per $\mu g/m^3$ of lead [70,179].

The situation in the occupational setting is somewhat different. Stankovic et al. [182] performed a cross-sectional study of 48 workers exposed to PbA levels ranging from 25 to 150 $\mu g/m^3$. The mean PbB level was 50 $\mu g/100$ mL (range 30-60 $\mu g/100$ mL). It is not clear how many workers were exposed to the higher PbA values.

Williams et al. [178] studied 39 lead-exposed workers using personal samplers. The authors found that with a PbA threshold limit value (TLV) of 200 $\mu g/m^3$, the mean PbB level was 70 $\mu g/100$ mL and for a PbA TLV of 150 $\mu g/m^3$, the mean PbB level was 60 $\mu g/100$ mL. The 95% confidence limits for PbB ranged up to 92 $\mu g/100$ mL and 82 $\mu g/100$ mL in each case respectively. In other words, a worker's PbB level could easily exceed 80 $\mu g/100$ mL for a PbA TLV of 150 $\mu g/m^3$. An α value of 30.1 $\mu g/100$ mL and a β value of 0.2 $\mu g/100$ mL per $\mu g/m^3$ were reported. The mean PbA exposures ranged from 9 $\mu g/m^3$ to 218 $\mu g/m^3$. Chamberlain [177] reanalyzed the Williams et al. [178] data from the reference point of

continuous exposure and derived a β value of 0.8 $\mu g/100$ mL per $\mu g/m^3$. Williams et al. [178] included lightly-exposed workers in their analysis with relatively low PbB values. If these "controls" were excluded, the calculated slope is estimated to be 0.12 [9]. Williams et al. [183] reported a problem with the personal sampler calibration during the investigations which could have resulted in systematic measurement error. The Williams et al. [178] mean values and confidence limits for single determinations of PbB level for certain PbA levels are presented in Table 6-I. The table also extrapolates his results to the lower levels of 100 $\mu g/m^3$ and 50 $\mu g/m^3$ and assumes a linear relationship at these lower levels.

King et al. [184] studied 65 lead-exposed male workers in three separate factories. Personal PbA samples and several biochemical parameters were examined including PbB level. The investigation was designed to test whether particle size distribution and solubility are important factors in the lead absorption of workers as might be expected. The authors found that the correlation coefficients were relatively low for all size/solubility combinations for PbA versus PbB levels, thus not supporting the original hypothesis. The authors presented the linear regressions for one particle size category and one solubility category only as well as for total PbA, representing the highest correlations observed. These correlation coefficients are presented in Table 6-II which includes descriptions of the particle size and solubility categories discussed. The linear correlation coefficients of PbA against the three PbA fractions were very similar with total PbA performing as well as any size/solubility combination. As stated by the authors, this does not necessarily mean that absorption is independent of particle size and solubility, but only that in the factories concerned, total PbA was as good a measure of "absorbed" lead as any of the fractions derived from it. It is postulated that larger lead particles deposited in the upper respiratory tract may be partially cleared by the muco-ciliary mechanism and ultimately make a significant

contribution to PbB level by absorption in the gastrointestinal tract.

Linear equations were also derived for these factories which gave α values of 46, 30, 52 $\mu g/100$ mL for corresponding β values of 0.032, 0.07 and 0.053 $\mu g/100$ mL per $\mu g/m^3$. The range of exposures of the workers studied by King et al. [184] was wide. Even after deletion of certain extreme outliers, the PbA level in two of the factories ranged up to approximately 450 and 800 $\mu g/m^3$. These high exposure levels are not comparable to usual occupational levels. Possible differences in particulate size distribution and individual worker's biological response at these high exposure levels could bias the PbA-PbB relationship so as not to be a good predictor for more usual occupational exposure levels. This bias would tend to lower the values of β.

Gartside et al. [185] examined 972 battery workers over 3 years. The authors used data obtained by personal sampling and assessed the relationship of this data to individual PbB levels obtained within 1 month of the exposure sample. 95% confidence limits were calculated for the prediction of PbB level given the PbA level for an individual worker. These results are indicated in Tables 6-III and 6-IV. The results emphasize the flattening of the curvilinear relationship between PbA and PbB levels at higher PbA levels. A β value of 0.05 $\mu g/100$ mL per $\mu g/m^3$ was found. The range of PbA level in the Gartside study was 25 to 350 $\mu g/m^3$. Strengths of this analysis included the large number of workers involved and the three year data collection period. As this work represented an analysis of regular monitoring data and not a study in itself, variability of sampling and analytic accuracy could have affected the reliability of the results although there is no obvious reason to make this assumption.

TABLE 6-I

MEAN VALUES AND 95% CONFIDENCE LIMITS (C.L.) OF SINGLE DETERMINATIONS OF PBB LEVEL CORRESPONDING TO PARTICULAR PBA LEVELS

PbA $\mu g/m^3$		PbB $\mu g/100$ mL
200	Mean	70
	95% C.L.	48 - 92
150	Mean	60
	95% C.L.	38 - 82
100*	Mean	50
	95% C.L.	28 - 72
50*	Mean	40
	95% C.L.	18 - 62

* Extrapolated from published results

From: Williams et al. (178)

TABLE 6-II

CORRELATION COEFFICIENT (R) OF PBA vs PBB FOR LINEAR REGRESSIONS

Factory	Total PbA		PbSize 6		PbSol 2	
	R	Significance of R	R	Significance of R	R	Signficance of R
1 n = 19	0.51	0.03	0.64	0.003	0.51	0.03
2 (a) n = 31	0.61	0.0001	0.50	0.004	0.64	0.0002
3 n = 48	0.24	0.10	0.24	0.10	0.24	0.10

2(a) = 3 outlying data points excluded.

PbSize 6 = largest particles retained in impactor (aerodynamic diameter 18 μm) of variable solubility; size based on cascade impactor separation.

PbSol 2 = particles soluble in water and 0.1N hydrochloric acid and of variable size fractions.

Extracted from King et al. (184)

A significant relationship between PbA and PbB levels was found although the amount of variation in PbB level that could be attributed to changes in PbA level was only 9%. Ingestion of lead, smoking, individual work habits and work history, individual biologic variability, and non-occupational sources of lead exposure are other possible determinants of PbB level. Area mobile air lead samples were not obviously related to PbB level. Gartside et al. (185) concluded that although there exists a positive relationship between PbA and PbB levels, the relationship is not sufficiently strong to use air lead measurements alone to protect the individual worker.

Bishop et al. (186) surveyed 233 lead-exposed workers. Using a curvilinear model of PbB versus PbA, the slope of the relationship varied from 0.02 to 0.06 with an average of 0.04 $\mu g/100$ mL per $\mu g/m^3$. The difference in PbA level was found to account for 10% of the variation in PbB level. After accounting for differences between specific work locations, the percentage had decreased to 2%. The authors roughly estimated that due to sampling variability in the observed air lead, they had underestimated the slope of PbB versus true lead exposure by 40%. A longitudinal analysis over 5 years yielded slopes ranging from 0.02 to 0.08 with an average of 0.05 $\mu g/100$ mL per $\mu g/m^3$. The authors tabulated the estimated % of workers having specific PbB levels above key PbA levels. This is reproduced as Table 6-V.

Snee (180) proposed a model to attempt to account for other sources of lead exposure apart from the PbA level and defined the PbB level by this equation:

$$PbB = K_1 (PbA + K_2)^{k_3}$$

where K_1, K_2, k_3 are parameters to be estimated from each data set. The necessity to know the values of these parameters and the inherent variability between workers of

TABLE 6-III

95% CONFIDENCE LIMITS FOR THE PREDICTED PBB LEVEL FOR AN INDIVIDUAL WORKER FOR A GIVEN PBA LEVEL

PbA	PbB
$\mu g/m^3$	95% Confidence Limits $\mu g/100$ mL
50	22 - 60
100	25 - 62
150	28 - 65
200	30 - 68

From: Gartside et al. (185)

TABLE 6-IV

EXPECTED PROPORTIONS OF PBB AT OR ABOVE SPECIFIED LEVELS BASED ON THE CORRESPONDING PBA LEVELS

PbA $\mu g/m^3$	PbB $\mu g/100$ mL				
	40	50	60	70	80
50	0.542	0.172	0.023	0.001	0.0002
100	0.652	0.252	0.042	0.003	0.0001
150	0.749	0.351	0.075	0.006	0.0002
200	0.828	0.461	0.126	0.014	0.0006

From: Gartside et al. (185)

TABLE 6-V

ESTIMATED % OF WORKERS HAVING PBB LEVELS ABOVE SPECIFIED LEVELS FOR CORRESPONDING PBA LEVELS

Plant	Blood Lead µg/100 mL	Air Lead Level (µg/m^3)			
		50	100	150	200
F (Best)	40	24	38	48	57
	50	4.6	9.9	15	21
	60	0.4	1.2	2.2	3.7
C (Typical)	40	48	57	64	69
	50	15	21	26	31
	60	2.2	3.7	5.3	7.1
D (Worst)	40	78	81	84	86
	50	42	46	50	54
	60	12	14	16	19

1978 Data
Workers not wearing respirators.
Best/Worst designation refers to an increasing percentage of workers above a specified PbB level for a given PbA level.

From: Bishop et al. (186)

the contribution to the PbB level of other factors limits the applicability of this model to groups of workers. Bishop et al. [186] concluded that although the Snee model provided a better fit for their data, the linear model provided an adequate approximation and that a slope β can be calculated in the neighbourhood of any particular PbA value on a curvilinear line.

The United States Occupational Safety and Health Administration (OSHA) [9] considered in great detail the PbA-PbB relationship including information submitted to them which was not found in the general literature. They also considered a theoretical model developed by an American agency, the Center for Policy Alternatives (CPA). The model, known as the Bernard model is based on the transfer of lead between various compartments within the mammalian body. The model takes into account particle size and job tenure, two potential problems with the cross-sectional analyses discussed earlier. To take particle size into consideration, the CPA assumed that the first 12.5 μg of lead in air is composed of particles less than or equal to 1 μm in diameter and all additional air particles are greater than or equal to 1 μm in diameter. OSHA believed the CPA-Bernard model to represent a synthesis of available information serving to define the PbA-PbB relationship. Table 6-VI is excerpted from the OSHA document which presents some of the occupational β values observed and the β values for given job tenures as predicted by the CPA-Bernard model.

The β values obtained from the other studies reviewed are summarized in Table 6-VII.

The cross-sectional analyses which explore the PbB-PbA relationship have some fundamental problems. Air lead is only one variable which determines blood lead level. Personal hygiene habits, smoking, recreational lead exposure, work procedures and individual biologic variability are other factors which may significantly

contribute to the PbB level. The variability of the contribution of these other sources is not assessed in a single cross-sectional analysis. In addition, differences in workers' life exposure histories, lead particulate type differences and physical work demand are factors which will cause β to vary across different cross-sectional analyses. If the effects of job tenure and particulate size were to be considered, the slope of the PbA-PbB relationship would tend to be higher. This is indeed reflected in the CPA-Bernard model as adopted by OSHA [9]. Finally, it should be noted that the curvilinear nature of the relationship implies that at lower levels of exposure, the effect of the PbA level on PbB level becomes greater as the slope of the relationship increases.

The limitations of the PbA-PbB data currently available mean that any approximation of the effects of a decrease in PbA level on PbB will be imprecise. OSHA [9] has approached the question somewhat differently and has calculated the % of workers having a given range of PbB levels for differing exposure levels. These are presented in Table 6-VIII. Froines et al. [187] have demonstrated that marked differences in the distribution of the PbB levels occur over that predicted by OSHA when the actual size distribution of the lead particulate is taken into account in a foundry and smelter setting. The findings are preliminary and require replication and further investigation in association with other factors such as changes in size distribution as a function of PbA concentration. They confirm the inadequacy of PbA alone as a means of protecting the worker and suggest that size-selective air sampling may be of use in certain circumstances in conjunction with biological monitoring measures.

TABLE 6-VI

β VALUES FOR A LINEAR PBA - PBB RELATIONSHIP

Source	Slope β
Globe-Union	0.1229
ASARCO (El Paso)	0.185
Delco-Remy	0.0628

β VALUES FOR A LINEAR PBA - PBB RELATIONSHIP

CPA-Bernard Model	
Job Tenure (years)	Slope β
0.95	0.1521
3.4	0.2062
9.0	0.2404
16.0	0.2604
28.5	0.2778

From: OSHA [9]

TABLE 6-VII

OCCUPATIONAL STUDIES OF THE PBA - PBB RELATIONSHIP

Author	Number of Workers	Range of PbA $\mu g/m^3$	Range of PbB $\mu g/100$ mL	Slope (β) $\mu g/m^3$ per $\mu g/100$ mL
Williams et al. (178) 1969	39	10 - 300	20 - 90	0.20
Stankovic et al. (182) 1971	48	25 - 150	30 - 60	——
King et al. (184) 1979 (3 Factories)	19 31 48	100 - 800 70 - 1150 30 - 330	35 - 70 25 - 80 20 - 90	0.032 0.070 0.053
Gartside et al. (185) 1982	972	10 - 360	22 - 70	0.0514
Bishop et al. (186) 1983	233	10 - 175 (Plant C)	20 - 60 (Plant C)	0.02 - 0.06* 0.02 - 0.08**

*Cross Sectional

**Longitudinal

It is seen that all of the published works respecting the PbA-PbB relationship have some weaknesses. However, the most recent works of Gartside et al. [185] and Bishop et al.[186] involved larger numbers of workers over relatively longer periods of time with exposure levels comparable to those occupational levels of interest and included some account for the effect of past lead exposure. The slopes of the PbA-PbB relationship were similar. The Williams et al.[178] study involved a small number of workers and involved systematic error due to incorrect calibration. King et al. [184] also used small numbers and very wide and often high exposure ranges. Gartside et al. [185] and Bishop et al. [186] therefore appear to be the stronger analyses. As shown in Tables 6-III, 6-IV and 6-VII, Gartside et al. [185] predict that 17% of workers would have a PbB level above 50 $\mu g/100$ mL at a PbA of 50 $\mu g/m^3$, whereas Bishop et al. [186] predict 15%, and OSHA [9] 6% for the same levels.

In Conclusion: It is seen that the PbA-PbB relationship is complex and is approximated by a curvilinear relationship which is not well defined. The slope of this relationship is variable but is less at occupational exposure levels than at community exposure levels by approximately a factor of 10 (1.0/0.1). This implies greater variability of the PbB level in relation to the PbA level at lower lead exposure levels.

The PbA level is only one determinant of the PbB level and depending on such factors as personal hygiene habits, smoking, recreational lead exposure, biological variability and work procedures, PbA level may be a relatively minor factor in the determination of PbB level. In addition, PbB levels are not only a measure of current absorption but also reflect body lead stores which may have accumulated from past lead exposure.

TABLE 6-VIII

% OF WORKERS HAVING CERTAIN PBB LEVELS FOR A GIVEN PBA LEVEL

PbB µg/100 mL	PbA µg/m^3	
	50	200
>60	0.5%	22.4%
50 - 60	5.5%	32.6%
40 - 50	23.3%	28.7%
Total % with PbB >50 µg/100 mL	6.0%	55.0%

From: OSHA (9)

Considering the above factors, the PbA level has a low probability of predicting the risk to the health of lead workers as measured by PbB levels and it cannot be used in place of PbB measurements as the prime method for monitoring the absorption of lead in the workplace.

However, there is a positive relationship between PbA and PbB levels and it is reasonable to conclude that a reduction in PbA level will effect some reduction in PbB level for most workers, the precise amount of which will depend on each worker and each situation. Estimations of the nature of the relationship between PbA and PbB levels have been presented and discussed in an effort to allow a rational choice of a permissable air lead level in Ontario. Reference to Tables 6-III, 6-IV, 6-V and 6-VIII provides an estimation of the expected proportions of workers having certain PbB levels for given PbA levels. These estimates should serve to guide the decision respecting an appropriate guideline for PbA levels in Ontario workplaces. From purely a medical standpoint, the most desirable approach would be to minimize the number of workers with PbB levels at or

above those levels considered inappropriate for Ontario workers in accordance with the concluding remarks of Section 7 and with the recommendations contained therein. Finally, and on more general grounds, the various other factors apart from PbA level which contribute to the PbB level must also be considered. Workers' hygienic habits and the occupational hygienic state of the workplace (e.g., dust accumulations) are factors of particular concern. Failure to consider these factors may negate any beneficial effects of a reduction in the current allowable PbA levels in effect in Ontario.

7. Concluding Remarks

Lead is a toxin with demonstrated multi-system effects in man. The effects of lead on certain organ systems have been researched in varying detail as evidenced by the differing quantity and quality of work in each area. Current knowledge in some areas is sparse and inconclusive thus limiting the usefulness of this knowledge to standard setting in the occupational setting. Other areas have been extensively researched, often from an occupational perspective. On occasion, dose-response relationships have been developed which have direct relevance to standard setting in the workplace.

7.1 Neurological Effects

The neurological effects of inorganic lead exposure have been one of the more widely researched areas. Detectable negative changes in neurobehavioural indices have been recorded in workers with blood lead levels in the range 40-60 μg/100 mL and occasionally at lower levels. Changes in neurophysiological function, in particular slowing of peripheral nerve conduction velocities have also been recorded in the range 40-60 μg/100 mL. Disagreement exists as to whether these neurological changes represent adverse health effects. Various aspects of the controversies involved have been discussed at the conclusions of Sections 5.2.1 and 5.2.2. Dose-response relationships for neurological effects in otherwise asymptomatic workers have been demonstrated in the literature. From one perspective, the changes may reasonably be interpreted as adverse health effects. The effects noted may be considered an early subclinical stage of clinical disease and have not been demonstrated to be reversible. They may also potentially enhance the susceptibility of the worker to the deleterious effects of other environmental influences. It may further be rationally hypothesized that the neurological changes observed, representing an effect on organ system function, may be more readily associated with an observable clinical

effect than would changes at a biochemical or cellular level.

Based on the neurological changes documented, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

A range for the blood lead level is chosen because the literature does not unequivocally support the choice of a precise value. Factors such as study design, including the choice of outcome measurements and measurement techniques, populations studied and biological variability are examples of possible reasons for the apparently inconsistent literature. From a prudent medical standpoint, it would be preferable for a worker's blood lead level to lie in the lower part of the range specified.

7.2 Effects on Heme Synthesis and the Erythropoietic System

The effects of lead on heme synthesis and the erythropoietic system have also been extensively researched and have been summarized at the conclusion of Section 5.1. The effects of lead on heme synthesis are measurable as changes in several biochemical parameters. These effects occur often at blood lead levels below 40 μg/100 mL and in the case of one heme-related enzyme (ALAD), the threshold level of lead exposure may be as low as zero. Through its effect on heme synthesis, lead has the potential to affect biochemical processes in many organ systems. Interpretation of these effects as adverse health effects is speculative and it remains possible that as yet undefined internal control mechanisms may maintain an adequate physiological homeostasis. A reduction in blood hemoglobin content represents one observable end point of the effects of lead on heme synthesis and the erythropoietic system. Although a blood lead threshold for lowering of hemoglobin content has not been conclusively established, a significant decrease of

hemoglobin content may occur for blood lead levels of 50-60 μg/100 mL in adults and probably at lower levels for children. This reduction is not necessarily synonymous with the occurrence of a clinically observable anemia. As with the neurological effects, a reduction in hemoglobin content represents a change in organ system function which is more closely associated with observable clinical effects on a continuum which extends from molecular, biochemical and cellular effects at one end to observable clinical effects at the opposite end.

Based on the effects on the hemoglobin content of blood, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies in the range 50-60 μg/100 mL (2.4-2.9 μmol/L).

7.3 Reproductive Effects

Lead is a reproductive toxin in sufficient dose. Low dose lead exposure has not been clearly associated with direct effects on the function of reproductive organs in either sex nor with teratogenic or mutagenic effects. Neurological fetotoxicity of low levels of lead exposure has been suggested. The critical question 'What is the upper level of lead exposure which should not be exceeded for the embryo or fetus in the workplace?' must be addressed. Studies attempting to relate embryonic/fetal lead exposure to subsequent developmental outcomes have been inconclusive and most have only presented preliminary results of long-term prospective endeavours. The studies do show the potential for an effect on developmental outcome in children due to prenatal and perinatal lead exposure at very low lead levels, in the approximate range of 10-30 μg/100 mL. It is not presently possible to relate the postulated effects of prenatal lead exposure to early effects on the embryo or later effects on the fetus. In this context, the term conceptus is used to cover all periods of human prenatal development. The conceptus is in a very active phase of central nervous system development and indeed, of total body

development compared to the adult. This fact alone calls for prudence when considering the upper level of exposure of the conceptus to lead particularly in the light of the multitude of toxicological effects of lead in several organ systems. Lead crosses the human placenta and neonatal umbilical cord blood lead levels correlate positively with and are similar to maternal blood lead levels. For practical purposes, limiting the blood lead level in the conceptus requires a similar limitation in the pregnant female.

Certain effects of lead have been noted to occur in children at lower levels of blood lead compared to adults. The child represents a physically independent organism whereas the conceptus represents a physically dependent organism supplied with maternal nutrients and enclosed in utero, a developmental environment vastly different from that of a child. These facts imply that the effects of lead on children may not necessarily be extrapolated to the conceptus. However, they do indicate the requirement for prudence when considering the issue of lead exposure for a developing organism such as the conceptus.

Based on the suspected prenatal neurotoxic effects and the requirement for prudence in exposing the developing conceptus to lead, the upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.4 μmol/L).

7.4 Renal Effects

Lead exposure has been associated with the development of renal disease. An adequate dose-response function between blood lead level and renal function has not been defined for chronic low dose lead exposure. The literature suggests that a blood lead level in the range 50-60 μg/100 mL maintained over time may be too high to protect workers from eventually developing clinically apparent kidney dysfunction.

Based on the renal effects, the upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded probably lies below 60 μg/100 mL (2.9 μmol/L).

7.5 Miscellaneous Health Effects

A causal relationship between lead and hypertension has not yet been established. Concern exists regarding the association of the blood lead level and blood pressure elevation but a dose-response relationship has not been clearly outlined in either animals or man. However, the current knowledge regarding hypertension and lead is inadequate to directly affect the setting of an upper limit of lead exposure in the occupational setting.

While certain lead salts are carcinogenic in some species of animal there is inadequate evidence that lead is carcinogenic in man.

Mortality studies have confirmed the vulnerability of certain organ systems to lead, in particular the renal system. Inherent difficulties with the mortality studies do not permit dose-response relationships to be defined, therefore limiting their usefulness for standard setting in the workplace.

The occurrence of clinical symptomatology confirms the possibility of organ dysfunction at low levels of lead exposure. However, the occurrence of symptoms is inadequate alone as a measure of lead exposure in the workplace.

The effects of lead on the endocrine and immune systems have been inadequately researched and any conclusions would be premature.

As a summary, Table 7-I presents the blood lead ranges supported by the literature for the first detectable biological effects due to inorganic lead exposure in adults.

TABLE 7-I

BLOOD LEAD LEVEL RANGES FOR FIRST DETECTABLE BIOLOGICAL EFFECTS IN ADULTS

PbB Level µg/100 mL	PbB Level µmol/L	Effect
0 - 15	(0 - 0.7)	ALAD inhibition.
20 - 35	(1.2 - 1.7)	Erythrocyte protoporphyrin elevation.
≤ 40	(≤ 1.9)	Blood and urinary ALA elevation.
40 - 60	(1.9 - 2.9)	Changes in neurobehavioural and neurophysiological functioning.
50 - 60	(2.4 - 2.9)	Decrease in hemoglobin content.
>80	(>3.9)	Acute lead poisoning.

The upper limit of the blood lead level which should not be exceeded is taken to be the maximum level at which an adverse health effect is unlikely to occur either acutely or chronically as a result of exposure over a working lifetime. Controversy exists as to which observed biological changes associated with lead exposure are to be considered adverse health effects. Rational criteria associated with adverse or non-adverse health effects have been outlined as guidelines and discussed in conjunction with the most relevant changes observed. The approach has been taken that when observed biological changes may reasonably be interpreted to be adverse health effects, the prudent course is to treat them as though they were. Based on these considerations and the current scientific evidence detailed in this document, the following recommendations are made:

The upper limit for the blood lead level in adult lead-exposed workers which should not be exceeded lies in the range 40-60 μg/100 mL (1.9-2.9 μmol/L).

The upper limit for the blood lead level in the conceptus which should not be exceeded probably lies in the range 10-30 μg/100 mL (0.5-1.5 μmol/L).

Where ranges of blood lead level have been specified, from a prudent medical standpoint it would be preferable for the blood lead level to lie in the lower part of the range specified.

Consideration should be given to the lowering of the current action levels for lead in blood as set out in the code for Medical Surveillance for lead in Ontario in Ontario Regulation 536/81.

The monitoring of the amount of lead per unit volume of urine on single samples is a less reliable means of monitoring lead exposure than blood lead levels. Where the taking of blood lead levels is deemed impractical or impossible, the concentration of lead in urine has been used to monitor lead exposure. Based on the considerations above and the relation of blood lead level to urine lead level as outlined in Appendix 3, the following proposal is made:

The upper limit for the concentration of lead in urine for adult lead-exposed workers which should not be exceeded lies in the range 6.3-11.2 μg/100 mL (0.30-0.54 μmol/L) or 33-73 μg Pb per g creatinine (0.16-0.35 μmol per g creatinine).

Because of the lower levels of lead exposure in the conceptus which should not be exceeded and because of the poorer validity and reliability of urine lead measurements, it is not recommended that urine lead monitoring be used to assess the lead exposure of the conceptus.

The lead exposure of the worker is dependent not only on air lead level but a number of other factors. It is reasonable to conclude that a reduction in the level of air lead may result in a reduction in the level of blood lead in the worker, although the amount of reduction may vary significantly between individual workers.

Based on the preceding recommendations and based on knowledge of the relationship between the concentration of lead in blood and the concentration of lead in air, consideration should be given to a lowering of the current air lead levels as set out in Ontario Regulation 536/81.

The science associated with the air lead-blood lead relationship has been discussed in this document. Because of the imprecise nature of this relationship, the setting of an appropriate air lead standard must be considered in a context broader than science alone, and as such no specific recommendation regarding an appropriate air lead standard is made herein.

Lead is perhaps the most extensively studied toxin in the scientific literature having been examined by a multitude of authors from numerous different perspectives. A multitude of interpretations of the vast amount of scientific data has resulted. A rational comprehensive consideration of the health effects of inorganic lead is therefore a difficult task. Ongoing monitoring of new scientific information is required. This document has presented an overview of the current issues involving the health effects of inorganic lead. The intent is to serve as a foundation for making informed decisions regarding the limits to be placed on lead exposure in the workplace.

8. Appendices

APPENDIX 1

Exerpts from the Regulation respecting Lead - made under the Occupational Health and Safety Act. Revised Statutes of Ontario, 1980. Chapter 321. Ontario Regulation 536/81.

RE: AIR LEAD LEVELS

Section 4.(1): Every employer shall take all necessary measures and procedures by means of engineering controls, work practices and hygiene practices and facilities to ensure that the time-weighted average exposure of a worker to airborne lead, except tetraethyl lead, shall not exceed 0.15 mg lead per m^3 of air, and in the case of exposure to tetraethyl lead 0.10 mg lead per m^3 of air.

Section 4.(2): In complying with subsection (1) the maximum concentration of exposure to airborne lead shall not exceed 0.30 mg lead per m^3 of air in the case of tetraethyl lead and 0.45 mg lead per m^3 of air in the case of lead other than tetraethyl lead and the exposure of a worker to such maximum concentration,

(a) shall not exceed fifteen minutes at any one time;

(b) shall not occur more than four times in a work day; and

(c) shall not occur until at least sixty minutes have elapsed from the time of the last previous exposure to such concentration.

RE: CODE FOR MEDICAL SURVEILLANCE FOR LEAD

Section 4.(1)(a): <u>Action Levels</u>

(i) <u>Lead in Blood</u>

Blood lead concentration is expressed as milligrams per litre of blood.

A concentration greater than 0.60 mg/L of lead in the blood requires enquiry regarding work practices and personal hygiene.

APPENDIX 1 (continued)

When the blood lead concentration of a worker is found to exceed 0.70 mg/L a further test must be undertaken immediately and if the result is confirmed the worker must be removed from lead exposure, although symptoms of lead intoxication are unlikely to be apparent at this level. If symptoms or signs of lead intoxication are present the worker must be removed from lead exposure regardless of blood lead level.

A determination by the physician must be made as to whether the worker is fit with limitations or unfit, and action taken in accordance with Section 16 of the Lead Regulation. Return to work may be permitted when the level of blood lead reaches 0.50 mg/L or less.

In order to safeguard a developing fetus a woman capable of bearing children must be removed from lead exposure when the blood lead concentration is found to exceed 0.40 mg/L.

(ii) Lead in Urine

Concentrations of lead in urine exceeding 0.15 mg/L are generally considered unacceptable, and when this level is exceeded the test must be repeated immediately to verify. If the result is confirmed in a worker exposed to tetraethyl or tetramethyl lead the worker must be removed from lead exposure. If the worker has been exposed to inorganic lead he may continue at work pending the result of an immediate blood specimen analysis and if the blood lead concentration exceeds 0.70 mg/L he must be removed from lead exposure.

In all cases a determination must be made by the physician as to whether the worker is fit with limitations or unfit, and action taken in accordance with Section 16 of the Lead Regulation. Return to work may be permitted if and when the level of blood lead reaches 0.50 mg/L or less in the case of workers exposed to inorganic lead, but for workers exposed to tetraethyl and tetramethyl lead the examining physician must determine fitness to return to work on the basis of his examination.

APPENDIX 2

ADVERSE (HEALTH) EFFECTS AS DEFINED BY A COMMITTEE OF THE US NATIONAL ACADEMY OF SCIENCES:

- "occur with intermittent or continued exposure and that result in impairment of functional capacity (as determined by anatomical, physiological, and biochemical, or behavioral parameters) or in a decrement of the ability to compensate for additional stress;
- are irreversible during exposure or following cessation of exposure if such changes cause detectable decrements in the ability of the organism to maintain homeostasis; and
- enhance the susceptibility of the organisms to the deleterious effects of other environmental influences."

NON-ADVERSE (HEALTH) EFFECTS AS DEFINED BY A COMMITTEE OF THE US NATIONAL ACADEMY OF SCIENCES:

- "changes that occur with continued exposure and do not result in impairment of functional capacity or the ability to compensate for additional stress;
- changes that are reversible following cessation of exposure, if such changes occur without detectable decrements in the ability of the organisms to maintain homeostasis; and
- changes that do not enhance the susceptibility of the organism to the deleterious effects of other environmental influences - chemical, physical, microbiological or social."

From: NAS (35)

APPENDIX 3

Measurement of Lead in Urine

The relationship of the concentration of lead in urine to the blood lead level has been investigated in different groups of occupationally lead-exposed workers. The regression equations from four separate studies of urine lead concentration as a function of blood lead concentration are as shown in Table A-3-I.

Using the different equations from each study, the predicted PbU values for PbB values ranging from 10-70 μg/100 mL are as shown in Table A-3-II.

It is clear that the linear relationships of Williams et al. (178) and Selander et al. (188) predict known false negative results at the low extremes of PbB level indicating the lack of validity of the linear model at very low levels of PbB. The study of Roels et al. (18) predicts a considerably higher urinary excretion of lead for female workers particularly at the higher levels of PbB. Mohammed-Brahim et al. (33) also found that lead-exposed women excrete significantly more lead in urine than do lead-exposed men. The curvilinear equations of King et al. (184) and Roels et al.(18) do not predict negative PbU levels at very low PbB levels.

Urinary lead absorption is less suitable than the PbB level as a test for lead absorption because of the influence of such factors as renal function, daily fluid intake and gender on urine lead content. This partially explains the differing results between studies.

It would be preferable not to use PbU determinations as a primary means of monitoring exposure to lead. If they are used, it would be reasonable and prudent to select the lower PbU values for given PbB values from the studies cited. This would only signal the possibility of an unacceptable PbB level and subsequent direct measurement of the PbB level would be required.

Based on the above reasoning and the values listed in Table A-3-II, a PbB level ranging from 40-60 μg/100 mL would be approximated by a PbU in the range 6.3-11.2 μg Pb per 100 mL urine (0.30-0.54 μmol/L) or 33-73 μg Pb per g creatinine (0.16-0.35 μmol per g creatinine).

TABLE A-3-I

RELATIONSHIP OF URINE LEAD LEVEL TO BLOOD LEAD LEVEL

Study	Regression Equation of PbU (ug/L) on PbB (ug/100 mL)	Population Studied
Williams et al. 1969 (178)	PbU = 2.46 PbB - 35.4	39 male lead-exposed workers and controls
Selander et al. 1984 (188)	PbU = 2.65 PbB - 33.1	177 lead-exposed workers and controls (sex not specified)

REGRESSION EQUATION OF PBU (ug/g CREATINNE) ON PBB ug/100 mL)

King et al. 1979 (184)	PbU = 0.67 PbB + 0.0099 $(PbB)^2$ + 8	82 lead-exposed workers
Roels et al. 1979 (18)	log PbU = 0.7234 + 0.0201 PbB	39 male lead-exposed workers (< 10 years exposure)
	log PbU = 0.8430 + 0.0170 PbB	60 male lead-exposed workers (>10 years exposure)
	log PbU = 0.5763 + 0.0349 PbB	36 female lead-exposed workers

TABLE A-3-II

PREDICTED PBU (ug/L) VALUES FOR GIVEN PBB VALUES

	PbB (ug/100 mL)						
Study	**10**	**20**	**30**	**40**	**50**	**60**	**70**
Williams et al. 1969 (178)	-10.8	13.8	38.4	63.0	87.6	112.2	136.8
Selander et al. 1970 (188)	-6.6	19.9	46.4	72.9	99.4	125.9	152.4

PREDICTED PBU (ug/g CREATININE) VALUES FOR GIVEN PBB VALUES

King et al. 1979 (184)		15.7	25.4	37.0	50.6	66.3	83.8	103.4
Roels et al. 1979 (18)	1	8.4	13.3	21.2	33.7	53.5	85.0	135.0
	2	10.3	15.2	22.5	33.3	49.2	72.9	107.9
	3	8.4	18.8	42.0	93.8	209.6	468.1	1045.4

9. References

1. Ontario Ministry of Labour. Occupational Health and Safety Division. The report on the designation of lead in Ontario, 1981.

2. Morrow PE, Beiter H et al. Pulmonary retention of lead: an experimental study in man. Environ Res 1980;21:373-384.

3. Rosen JF. Metabolic and cellular effects of lead: a guide to low level lead toxicity in children. In: Dietary and environmental lead: human health effects. Mahaffey (ed.). Elsevier Science Publishers BV 1985;157-185.

4. Manton WI, Cook JD. High accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br J Ind Med 1984;41:313-319.

5. Hryhorczuk DO, Rabinowitz MB et al. Elimination kinetics of blood lead in workers with chronic lead intoxication. Am J Ind Med 1985;8:33-42.

6. O'Flaherty EJ, Hammond PB et al. Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fund Appl Tox 1982; 2:49-54.

7. Wolff MS. Occupationally derived chemicals in breast milk. Am J Ind Med 1983; 4:259-281.

8. Rabinowitz M, Leviton A et al. Lead in milk and infant blood: a dose-response model. Arch Environ Health 1985; 40(5):283-286.

9. United States. Occupational Health and Safety Administration. Occupational safety and health standards: occupational exposure to lead. Fed Reg 1978;43(225):54354-54509.

10. Moore MR, Goldberg A. Health implications of the hematopoietic effects of lead. In: Dietary and environmental lead: human health effects. Mahaffey (ed.). Elsevier Science Publishers BV 1985;261-314.

11. World Health Organization. Environmental Health Criteria 3. Lead. Geneva 1977.

12. Zielhuis RL. Dose response relationships for inorganic lead. Int Arch Occup Health 1975;35:1-18.

13. Meredith P, Moore M et al. Delta-aminolaevulinic acid metabolism in normal and lead-exposed humans. Toxicology 1978;9:1-9.

14. Joselow MM, Flores J. Application of the zinc protoporphyrin (ZP) test as a monitor of occupational exposure to lead. Am Ind Hyg Assoc J 1977;38:63-66.

15. Grandjean P, Lintrup J. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. Scand J Clin Lab Invest 1978;38:669-675.

16. Herber R. Estimation of blood lead values from blood porphyrin and urinary 5-aminolevulinic acid levels in workers. Int Arch Occup Environ Health 1980;45:169-179.

17. Zielhuis RL. Second International Workshop. Permissible levels for occupational exposure to inorganic lead. Int Arch Occup Environ Health 1977; 39:59-72.

18. Roels HA, Balis-Jacques MN et al. The influence of sex and chelation therapy on erythrocyte protoporphyrin and urinary δ-aminolevulinic acid in lead-exposed workers. J Occup Med 1979;21(8):527-539.

19. Piomelli S, Seaman C et al. Threshold for lead damage to heme synthesis in urban children. Proc Natl Acad Sci USA 1982;79:3335-3339.

20. Mahaffey KR. Factors modifying susceptibility to lead toxicity. In: Dietary and environmental lead: human health effects. Mahaffey (ed.). Elsevier Science Publishers BV 1985;373-419.

21. Mahaffey KR, Rosen JF et al. Association between age, blood lead concentration, and serum 1,25-dihydroxycholecaliciferol levels in children. Am J Clin Nutr 1982;35:1327-1331.

22. Greenberg A, Landrigan PJ et al. Effects of elevated lead and cadmium burdens on renal function and calcium metabolism. Arch Environ Health 1986;41(2):69-76.

23. Saenger P, Markowitz ME et al. Depressed excretion of 6ß-hydroxycortisol in lead-toxic children. J Clin Endocrinol Metab 1984;58(2):363-367.

24. Silbergeld EK, Lamon JM. Role of altered heme synthesis in lead neurotoxicity. J Occup Med 1980;22(10):680-684.

25. Hammond PB, Lerner SI et al. The relationship of biological indices of lead exposure to the health status of workers in a secondary lead smelter. J Occup Med 1980;22(7):475-484.

26. Hernberg S. Biochemical and clinical effects and responses as indicated by blood concentration. In: Singhal RL and Thomas (eds.). Lead Toxicity. Urban and Schwarzenberg. Baltimore 1980;367-399.

27. Grandjean P. Occupational lead exposure in Denmark: screening with the haematofluorometer. Br J Ind Med 1979;36:52-58.

28. Baker EL, Landrigan PJ et al. Occupational lead poisoning in the United States: clinical and biochemical findings related to blood lead levels. Br J Ind Med 1979;36:314-322.

29. Valentine JL, Baloh RW et al. Subclinical effects of chronic increased lead absorption - a prospective study. Part IV. Evaluation of heme synthesis effects. J Occup Med 1982;24(2):120-125.

30. Tola S, Hernberg S et al. Parameters indicative of absorption and biological effect in new lead exposure: a prospective study. Br J Ind Med 1973;30:134-141.

31. Betts PR, Astley R et al. Lead intoxication in children in Birmingham. Br Med J 1973;1:402-406.

32. Paglia DE, Valentine WN. Hereditary and acquired defects in the pyrimidine nucleotidase of human erythrocytes. Curr Top Hematol 1980;3:75-109.

33. Mohammed-Brahim B, Buchet JP et al. Erythrocyte pyrimidine-5'-nucleotidase activity in workers exposed to lead, mercury or cadmium. Int Arch Occup Environ Health 1985;55:247-252.

34. Lachant NA, Tomoda A et al. Inhibition of the pentose phosphate shunt by lead: a potential mechanism for hemolysis in lead poisoning. Blood 1984;63(3):518-524.

35. Report of the Committee for the Working Conference on Principles of Protocols for Evaluating Chemicals in the Environment. US National Academy of Sciences. Washington DC, 1975;124-126.

36. Repko JD, Corum CR. Critical review and evaluation of the neurological and behavioural sequelae of inorganic lead absorption. CRC Crit Rev Toxicol 1979;6:135-187.

37. Valciukas JA, Lilis R et al. Lead exposure and behavioural changes: comparisons of four occupational groups with different levels of lead absorption. Am J Ind Med 1980;1:421-426.

38. Arnvig E, Grandjean P et al. Neurotoxic effects of heavy lead exposure determined with psychological tests. Toxicol Lett 1980;5:399-404.

39. Mantere P, Hanninen H et al. Subclinical neurotoxic lead effects: two year follow-up studies with psychological test methods. Neurobehav Toxicol Teratol 1982;4(6):725-727.

40. Mantere P, Hanninen H et al. A prospective follow-up study on psychological effects in workers exposed to low levels of lead. Scand J Work Environ Health 1984;10:43-50.

41. Baker EL, Feldman RG et al. The role of occupational lead exposure in the genesis of psychiatric and behavioural disturbances. Acta Psychiat Scand 1983;67 Suppl 303:38-48.

42. Baker EL, Feldman RG et al. Occupational lead neurotoxicity: a behavioural and electrophysiological evaluation. Study design and year one results. Br J Ind Med 1984;41:352-361.

43. Baker EL, White RF et al. Occupational lead neurotoxicity: improvement in behavioural effects after reduction of exposure. Br J Ind Med 1985;42:507-516.

44. Hogstedt C, Hane M et al. Neuropsychological test results and symptoms among workers with well-defined long-term exposure to lead. Br J Ind Med 1983;40:99-105.

45. Campara P, D'Andrea F et al. Psychological performance of workers with blood-lead concentration below the current threshold limit value. Int Arch Occup Environ Health 1984;53:233-246.

46. Zimmerman-Tansella C, Campara P et al. Psychological and physical complaints of subjects with low exposure to lead. Human Toxicol 1983;2:615-623.

47. Parkinson DK, Ryan C et al. A psychiatric epidemiologic study of occupational lead exposure. Am J Epi 1986;123(2):261-269.

48. Araki S, Yokoyama K et al. Psychological performance in relation to central and peripheral nerve conduction in workers exposed to lead, zinc and copper. Am J Ind Med 1986;9:535-542.

49. Williamson AM, Teo RKC. Neurobehavioural effects of occupational exposure to lead. Br J Ind Med 1986; 43:374-380.

50. Silbergeld EK. Experimental studies of lead neurotoxicity: implications for mechanisms, dose-response and reversibility. In: Lead versus health. Rutter and Russell Jones (eds.). John Wiley and Sons Ltd 1983;191-216.

51. Rice DC, Gilbert SG. Low lead exposure from birth produces behavioural toxicity (DRL) in monkeys. Toxicol Appl Pharmacol 1985;80:421-426.

52. Araki S, Honma T et al. Recovery of slowed nerve conduction velocity in lead-exposed workers. Int Arch Occup Environ Health 1980;46:151-157.

53. Ashby JAS. A neurological and biochemical study of early lead poisoning. Br J Ind Med 1980;37:133-140.

54. Spivey GH, Baloh RW et al. Subclinical effects of chronic increased lead absorption - a prospective study. III. Neurologic findings at follow-up examination. J Occup Med 1980;22(9):607-612.

55. Seppalainen AM, Hernberg S. Subclinical lead neuropathy. Am J Ind Med 1980;1:413-420.

56. Seppalainen AM, Hernberg S. A follow-up study of nerve conduction velocities in lead exposed workers. Neurobehav Tox Teratol 1982;4:721-723.

57. Seppalainen AM, Hernberg S et al. Early neurotoxic effects of occupational lead exposure: a prospective study. Neurotoxicology 1983;4(2):181-192.

58. Bordo BM, Fillipini G. Electrophysiological study of subjects occupationally exposed to lead and with low levels of lead poisoning. Scand J Work Environ Health 1982;8(suppl 1):142-147.

59. Nielsen CJ, Nielsen VK et al. Absence of peripheral neuropathy in long-term lead-exposed subjects. Acta Neurol Scandinav 1982; 65:241-247.

60. Sborgia G, Assennato G et al. Comprehensive neurophysiological evaluation of lead-exposed workers. In: Neurobehavioural methods in occupational health, 1982. Proceedings of the international symposium on neurobehavioural methods in occupational health. Gilioli, Cassito and Foa (eds.). Pergamon Press, New York 1983;283-294.

61. Rosen I, Wildt K et al. Neurophysiological effects of lead exposure. Scand J Work Environ Health 1983;9:431-441.

62. Singer R, Valciukas JA et al. Lead exposure and nerve conduction velocity: the differential time course of sensory and motor nerve effects. Neurotoxicology 1983;4(2):193-202.

63. Corsi S, Bartolucci GB et al. Biochemical and electrophysiological study of subjects with a history of past lead exposure. Am J Ind Med 1984;6:281-290.

64. Triebig G, Weltle D et al. Investigations on neurotoxicity of chemical substances at the workplace. Arch Occup Environ Health 1984;53:189-204.

65. Jeyaratnam J, Devathasan G et al. Neurophysiological studies on workers exposed to lead. Br J Ind Med 1985;42:173-177.

66. Chen ZQ, Chan QI et al. Peripheral nerve conduction velocity in workers occupationally exposed to lead. Scand J Work Environ Health 1985; 11(suppl 4):26-28.

67. Araki S, Yokoyama K. et al. Determination of the distribution of conduction velocities in workers exposed to lead, zinc, and copper. Br J Ind Med 1986;43:321-326.

68. Cavalleri A, Trimarchi F et al. Effects of lead on the visual system of occupationally exposed subjects. Scand J Work Environ Health 1982;8(suppl 1):148-151.

69. Glickman L, Valciukas JA et al. Occupational lead exposure. Effects on saccadic eye movements. Int Arch Occup Environ Health 1984;54:115-125.

70. Landrigan PJ, Froines JR et al. Body lead burden: summary of epidemiological data on its relation to environmental sources and toxic effects. In: Dietary and environmental lead: human health effects. Mahaffey (ed.). Elsevier Science Publishers BV 1985;421-451.

71. Clarkson TW, Nordberg GF et al. Reproductive and developmental toxicity of metals. Scand J Work Environ Health 1985;11:145-154.

72. Thomas JA, Brogan WC. Some actions of lead on the sperm and on the male reproductive system. Am J Ind Med 1983;4:127-134.

73. Willems MI, de Schepper GG et al. Absence of an effect of lead acetate on sperm morphology, sister chromatid exchanges on micronuclei formation in rabbits. Arch Toxicol 1982;50:149-157.

74. Wiebe JP, Barr KJ et al. Lead administration during pregnancy and lactation affects steroidogenesis and hormone receptors in testes of offspring. J Toxicol Environ Health 1982;10:653-666.

75. Sokol RZ, Madding CE et al. Lead toxicity and the hypothalamic-pituitary-testicular axis. Biol Reprod 1985;33:722-728.

76. Chowdhury AR, Dewan A et al. Toxic effects of lead on the testes of rat. Biomed Biochim Acta 1984;43(1):95-100.

77. McCauley PT, Bull RJ et al. The effect of prenatal and postnatal lead exposure on neonatal synaptogenesis in rat cerebral cortex. J Toxicol Environ Health 1982;10:639-651.

78. Miller CD, Buck WB et al. Fetal rat development as influenced by maternal lead exposure. Vet Hum Toxicol 1982;24(3):163-166.

79. Hayashi M. Lead toxicity in the pregnant rat. II. Effects of low-level lead on δ-aminolevulinic acid dehydratase activity in maternal and fetal blood or tissue. Indust Health 1983;21:127-135.

80. Wardell RE, Seegmiller RE et al. Induction of prenatal toxicity in the rat by diethylstilbestrol, zeranol, 3,4,3',4'-tetrachlorobiphenyl, cadmium and lead. Teratology 1982;26:229-237.

81. Hackett PL, Hess JO et al. Distribution and effects of intravenous lead in the fetoplacental unit of the rat. J Toxicol Environ Health 1982; 9:1021-1032.

82. Minsker DH, Moskalski N et al. Exposure of rats to lead nitrate in utero or postpartum; effects on morphology and behaviour. Biol Neonate 1982;41:193-203.

83. Wide M. Lead exposure on critical days of fetal life affects fertility in the female mouse. Teratology 1985;32(3):375-380.

84. Carpenter SJ. Enhanced teratogenicity of orally administered lead in hamsters fed diet deficient in calcium or iron. Toxicology 1982;24:259-271.

85. Wildt K, Eliasson R et al. Effects of occupational exposure to lead on sperm and semen. In: Clarkson, Norberg and Sager (eds.). Reproductive and developmental toxicity of metal. New York Plenum Press 1983;279-300.

86. Butrimovitz GP, Sharlip I et al. Extremely low seminal lead concentration and male fertility. Clin Chim Acta 1983;135:229-231.

87. Cullen MR, Kayne RD et al. Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. Arch Environ Health 1984;39(6):431-440.

88. Uzych L. Teratogenesis and mutagenesis associated with the exposure of human males to lead: a review. Yale J Biol Med 1985;58:9-17.

89. Saric M. Reproduction and exposure to lead. Ann Acad Med Singapore 1984;13(2)(suppl):383-388.

90. Needleman HL, Rabinowitz M et al. The relationship between prenatal exposure to lead and congenital anomalies. JAMA 1984;251(22):2956-2959.

91. McMichael AJ, Vimpani GV et al. The Port Pirie cohort study: maternal blood lead and pregnancy outcome. J Epidemiol Comm Health 1986;40:18-25.

92. Maki-Paakkanen J, Sorsa M et al. Chromosome aberrations and sister chromatid exchanges in lead-exposed workers. Hereditas 1981;94:269-275.

93. Grandjean P, Wulf HC et al. Sister chromatid exchange in response to variations in occupational lead exposure. Environ Res 1983;32:199-204.

94. Beckman L, Nordenson I et al. Occupational and environmental risks in and around a smelter in northern Sweden. VIII. Three-year follow-up of chromosomal aberrations in workers exposed to lead. Heriditas 1982;96:261-264.

95. Garza-Chapa R, Leal-Garza C et al. Population genetics in the state of Nuevo Leon, Mexico. II. Genetic markers, frequencies and their possible association with chromosomic damage in workers exposed to lead. Arch Invest Med Mex 1980;11:547-559.

96. Forni A. Chromosomal effects of lead. A critical review. Rev Environ Health 1980;3(2):114-129.

97. Forni A, Sciame A et al. Chromosome and biochemical studies in women occupationally exposed to lead. Arch Environ Health 1980;35(3):139-146.

98. Hoffman M, Hagberg S et al. Inorganic lead exposure does not effect lymphocyte micronuclei in car radiator repair workers. Hereditas 1984;101:223-226.

99. Barltrop D. Transfer of lead to the human foetus. In: Mineral Metabolism in Paediatrics. Barltrop and Barland (eds.). Philadelphia 1969;135-151.

100. Khera AK, Wibberley DG et al. Placental and stillbirth tissue lead concentrations in occupationally exposed women. Br J Ind Med 1980; 37:394-396.

101. Alexander FW, Delves HT. Blood lead levels during pregnancy. Int Arch Occup Environ Health 1981;48:35-39.

102. Bonithon-Kopp C, Huel G et al. Effects of pregnancy on the inter-individual variations in blood levels of lead, cadmium and mercury. Biol Res Preg Perinatol 1986;7(1):37-42.

103. Ong CN, Lee WR. High affinity of lead for fetal haemoglobin. Br J Ind Med 1980;37:292-298.

104. Borella P, Picco P et al. Lead content in abortion material from urban women in early pregnancy. Int Arch Occup Environ Health 1986;57:93-99.

105. Ghafour SY, Khuffash FA et al. Congenital lead intoxication with seizures due to prenatal exposure. Clin Pediatr (Phila) 1984;23(5):282-283.

106. Bellinger DC, Needleman HL et al. Early sensory-motor development and prenatal exposure to lead. Neurobehav Toxicol Teratol 1984;6:387-402.

107. Bellinger DC, Leviton A et al. Low-level lead exposure and infant development in the first year. Neurobehav Toxicol Teratol 1986;8:151-161.

108. Bornschien RL, Hammond PB et al. The Cincinnati prospective study of low-level lead exposure and its effects on child development protocol and status report. Environ Res 1985;38:4-18.

109. Dietrich KN, Krafft KM et al. Postnatal lead exposure and early sensorimotor development. Environ Res 1985;38:130-136.

110. Padich RA, Dietrich KN et al. Attention, activity level, and lead exposure at 18 months. Environ Res 1985;38:137-143.

111. Moore MR, Goldberg A et al. A prospective study of the neurological effects of lead in children. Neurobehav Toxicol Teratol 1982;4(6):739-743.

112. Starr RH. Current research on the developmental ecology of lead exposure during childhood. Environ Res 1985;38:197-210.

113. Moore MR, Goldberg A et al. Some studies of maternal and infant lead exposure in Glasgow. Scott Med J 1982;27:113-122.

114. Winneke G, Beginn U et al. Comparing the effects of perinatal and later childhood lead exposure on neuropsychological outcome. Environ Res 1985;38: 155-167.

115. Vimpani G, McMichael A et al. The Port Pirie study: A prospective study of pregnancy outcome and early childhood growth and development in a lead-exposed community - protocol and status report. Environ Res 1985;38:19-23.

116. Ernhart CB, Wolf AW et al. Fetal lead exposure: antenatal factors. Environ Res 1985;38:54-66.

117. Bonithon-Kopp C, Huel G et al. Prenatal exposure to lead and cadmium and psychomotor development of the child at six years. Neurobehav Toxicol Teratol 1986;8(3):307-310.

118. Wedeen RP, Mallik DK et al. Detection and treatment of occupational lead nephropathy. Arch Intern Med 1979;139:53-57.

119. Lilis R, Fischbein A et al. Kidney function and lead: relationships in several occupational groups with different levels of exposure. Am J Ind Med 1980;1:405-412.

120. Hong CD, Hanenson IB et al. Occupational exposure to lead: effects on renal function. Kidney Int 1980;18:489-494.

121. Buchet JP, Roels H et al. Assessment of renal function of workers exposed to inorganic lead, cadmium or mercury vapor. J Occup Med 1980;22(11):741-750.

122. Batuman V, Maesaka JK et al. The role of lead in gout nephropathy. New Engl J Med 1981;304(9):520-523.

123. Wright LF, Saylor RP et al. Occult lead intoxication in patients with gout and kidney disease. J Rheumatol 1984;11:517-520.

124. Behringer D, Craswell P et al. Urinary lead excretion in uremic patients. Nephron 1986;42:323-329.

125. Campbell BC, Elliott HL et al. Lead exposure and renal failure: does renal insufficiency influence lead kinetics? Toxicol Lett 1981;9:121-124.

126. Meyer BR, Fischbein A et al. Increased urinary enzyme excretion in workers exposed to nephrotoxic chemicals. Am J Med 1984;76:989-998.

127. Dingwall-Fordyce I, Lane RE. A follow-up study of lead workers. Br J Ind Med 1963;20:313-315.

128. Cramer K, Dahlberg L. Incidence of hypertension among lead workers. Br J Ind Med 1966;23:101-104.

129. Malcolm D. Prevention of long-term sequelae following the absorption of lead. Arch Environ Health 1971;23:292-298.

130. Beattie AD, Moore MR et al. Environmental lead pollution in an urban soft-water area. Br Med J 1972;27:491-493.

131. Beevers DG, Erskine E et al. Blood-lead and hypertension. Lancet 1976;2:1-3.

132. Rogan WJ, Hogan MD et al. Blood pressure and lead levels in children. J Environ Pathol Toxicol 1978;2(2):517-519.

133. Jhaveri RC, Lavorgna L et al. Relationship of blood pressure to blood lead concentrations in small children. Ped 1979;63(4):672-676.

134. Frielander MA, Brooks CT et al. Blood pressure and creatinine clearance in lead-exposed children: the effect of treatment. Arch Environ Health 1981;36(6):310-315.

135. Batuman V, Landy E et al. Contribution of lead to hypertension with renal impairment. N Engl J Med 1983;309(1):17-21.

136. Pocock SJ, Shaper AG et al. Blood lead concentration, blood pressure and renal function. Br Med J 1984;289:872-874.

137. Sparrow D, Sharrett AR et al. Trace metals in drinking water: lack of influence on blood pressure. J Chron Dis 1984;37(1):59-65.

138. Staessen J, Bulpitt CJ et al. Urinary cadmium and lead concentrations and their relationship to blood pressure in a population with low exposure. Br J Ind Med 1984;41:241-248.

139. Kromhout D, Wibowo AAE et al. Trace metals and coronary heart disease risk indicators in 152 elderly men (the Zutphen study). Am J Epi 1985;122(3):378-385.

140. Orssaud G, Claude JR et al. Blood lead concentration and blood pressure. Br Med J 1985;290:244.

141. Harlan WR, Landis JR. Blood lead and blood pressure. Relationship in the adolescent and adult U.S. population. JAMA 1985;253(4):530-534.

142. Pirkle JL, Schwartz J et al. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epi 1985;121(2):246-258.

143. Kirkby H, Gyntelberg F. Blood pressure and other cardiovascular risk factors of long-term exposure to lead. Scand J Work Environ Health 1985;11:15-19.

144. Cooper WC, Wong O et al. Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand J Work Environ Health 1985;11(5):331-345.

145. Weiss ST, Munoz A. The relationship of blood lead to blood pressure in a longitudinal study of working men. Am J Epidemiol 1986;123(5):800-808.

146. Kopp SJ, Perry HM et al. Cardiac physiologic-metabolic changes after chronic low level heavy metal feeding. Am J Physiol 1980;239:H22-H30.

147. Aviv A, John E et al. Lead intoxication during development: its late effects on kidney function and blood pressure. Kidney Int 1980;17:430-437.

148. Revis NW, Zinmeister AR et al. Atherosclerosis and hypertension induction by lead and cadmium ions: an effect prevented by calcium ion. Proc Natl Acad Sci USA 1981;78(10):6494-6498.

149. Victery W, Vander AJ et al. Lead, hypertension and the renin-angiotensin system in rats. J Lab Clin Med 1982;99(3):354-362.

150. Victery W, Vander AJ et al. Lead exposure, begun in utero, decreases renin and angiotensin II in adult rats (41398). Proc Soc Exp Biol Med 1982;170:63-67.

151. Victery W, Vander AJ et al. Plasma renin is increased in young rats exposed to lead in utero and during nursing (41517). Proc Soc Exp Biol Med 1983;172:1-7.

152. Campbell BC, Meredith PA et al. Lead exposure and change in the renin-angiotensin-aldosterone system in man. Toxicol Lett 1985;25:25-32

153. Baker EL, Goyer RA et al. Occupational lead exposure, nephropathy and renal cancer. Am J Ind Med 1980;1:139-148.

154. Lilis R. Long-term occupational lead exposure, chronic nephropathy and renal cancer: a case report. Am J Ind Med 1981;2:293-297.

155. International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemicals, Industrial Processes and Industries Associated with Human Cancer. IARC Monographs. 1982;Supplement 4:149-150.

156. Kazantzis G. Role of cobalt, iron, lead, manganese, mercury, platinum, selenium and titanium in carcinogenesis. Environ Health Perspec 1981;40:143-161.

157. Cooper WC, Gaffey WR. Mortality of lead workers. J Occup Med 1975;17:100-107.

158. Kang HK, Infante PF et al. Occupational lead exposure and cancer. Science 1980;207:935-937.

159. McMichael AJ, Johnson HM. Long-term mortality profile of heavily-exposed lead smelter workers. J Occup Med 1982;24:375-378.

160. Malcolm D, Barnett HA. A mortality study of lead workers 1925-76. Br J Ind Med 1982;39:404-410.

161. Selevan SG, Landrigan PJ et al. Mortality of lead smelter workers. Am J Epidemiol 1985;122(4):673-683.

162. Reigart JR, Graber CD. Evaluation of the humoral immune response of children with low level lead exposure. Bull Environ Contam Toxicol 1976;16:112-117.

163. Sachs HK. Intercurrent infection in lead poisoning. Am J Dis Child 1978;132:315-316.

164. Ewers U, Stiller-Winkler R et al. Serum immunoglobulin, complement C_3, and salivary IgA levels in lead workers. Environ Res 1982;29:351-357.

165. Koller LD. Immunological effects of lead. In: Dietary and environmental lead: human health effects. Mahaffey (ed.). Elsevier Science Publishers BV 1985;339-353.

166. Robins JM, Cullen MR et al. Depressed thyroid indexes associated with occupational exposure to inorganic lead. Arch Intern Med 1983;143:220-224.

167. Refowitz RM. Thyroid function and lead. No clear relationship. J Occup Med 1984;26:579-583.

168. Hanninen H, Mantere P et al. Subjective symptoms in low-level exposure to lead. Neurotoxicology 1979;1:333-347.

169. Spivey GH, Brown CP et al. Subclinical effects of chronic increased lead absorption - a prospective study. I. Study design and analysis of symptoms. J Occup Med 1979;21(6):423-429.

170. Fischbein A, Thornton JC et al. Zinc protoporphyrin, blood lead and clinical symptoms in two occupational groups with low-level exposure to lead. Am J Ind Med 1980;1:391-399.

171. Cullen MR, Robins JM et al. Adult inorganic lead intoxication: Presentation of 31 new cases and a view of recent advances in the literature. Medicine 1983;62(4):221-247.

172. Williams MK, Walford J et al. Blood lead and the symptoms of lead absorption. Br J Ind Med 1983;40:285-292.

173. Neri LC, Hewitt D et al. Health effects of low level occupational exposure to lead: The Trail, British Columbia study. Arch Environ Health 1983;38:180-189.

174. Kirkby H, Nielsen CJ et al. Subjective symptoms after long term lead exposure in secondary lead smelting workers. Br J Ind Med 1983;40:314-317.

175. Wang YL, Lu PK et al. Effects of occupational lead exposure. Scand J Work Environ Health 1985;11(suppl 4):20-25.

176. Hammond PB, O'Flaherty EJ et al. The impact of air-lead on blood-lead in man. A critique of the recent literature. Fd Cosmet Toxicol 1981;19:631-638.

177. Chamberlain AC. Effect of airborne lead on blood lead. Atmos Environ 1983;17(4):677-692.

178. Williams MK, King E et al. An investigation of lead absorption in an electric accumulator factory with the use of personal samplers. Br J Ind Med 1969;26:202-216.

179. Snee RD. Evaluation of studies of the relationship between blood lead and air lead. Int Arch Occup Environ Health 1981;48:219-242.

180. Snee RD. Models for the relationship between blood lead and air lead. Int Arch Occup Environ Health 1982;50:303-319.

181. United States Department of Health, Education and Welfare. National Institute for Occupational Safety and Health (NIOSH) 1978. Criteria for a recommended standard for occupational exposure to inorganic lead. Publication No. 78-158.

182. Stankovic MK. Biochemical tests for the appraisal of exposure to lead. Arch Environ Health 1971;23:265-269.

183. Williams MK. Permissible limits for occupational exposure to inorganic lead and the blood lead-air lead relationship. Int Arch Occup Environ Health 1978; 41:151-157.

184. King E, Conchie D et al. Industrial lead absorption. Ann Occup Hyg 1979;22:213-239.

185. Gartside PS, Buncher CR et al. Relationship of air lead and blood lead for workers at an automobile battery factory. Int Arch Occup Environ Health 1982;50:1-10.

186. Bishop L, Hill WJ. A study of the relationship between blood lead levels and occupational air lead levels. The Am Statistician 1983;37(4):471-475.

187. Froines JR, Liu WCV et al. Effect of aerosol size on the blood lead distribution of industrial workers. Am J Ind Med 1986;9:227-237.

188. Selander S, Cramer K. Interrelationships between lead in blood, lead in urine and ALA in urine during lead work. Br J Ind Med 1970;27:28-39.